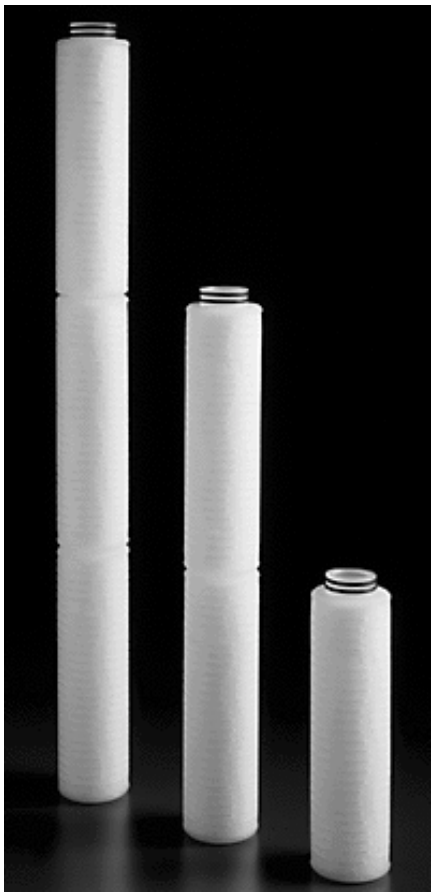
Minimum Bubble Point Specification for Sterilizing-Grade 0.22 µm Durapore® Membranes



Millipore is increasing the minimum bubble point specification of sterilizing-grade (0.22 µm) Durapore membrane from 45 psig (3100 mbarg) to 50 psig (3450 mbarg) in response to a recent regulatory trend to have bacterial retention validation studies performed using membranes at or near the filter manufacturer's minimum production limit.

Millipore has made no change to the membrane or how it is manufactured. The bubble point specification has been moved to within our manufacturing range.

Recent Industry Initiatives

Sterilizing filtration, as a method of preparing safe and sterile drug products, has evolved and gained confidence through more stringent validation practices and new guidance documents.

This evolution has been stimulated by a number of industry initiatives over the past years. One major event has been the publication by the Parenteral Drug Association (PDA) of the Technical Report No. 26, *Sterilizing Filtration of Liquids*, which provides a systematic approach to selecting and validating the most appropriate sterilizing-grade filter.

The PDA Technical Report No. 26 references acceptance criteria for representative membranes to be used in bacterial retention validation studies (1).

"Filter membrane lots used for bacterial retention validation should have a pre-filtration, water wet, physical integrity test value at or near the filter manufacturer's production limit. Other filter parameters, including thickness, should be representative of typical production membranes."

Recent Regulatory Trends

Sterilizing filtration has been under increasing regulatory scrutiny for the last decade, with the emergence of more stringent validation requirements. Recent regulatory observations have shown that FDA inspects the validation of sterilizing-grade filtration to acceptance criteria as described in the PDA Technical Report No. 26.

The FDA observations on NDA submissions summarized below have questioned the validity of a product-specific bacterial retention test performed on membranes with a significantly higher bubble point than the one specified in the drug manufacturing process, and have recommended the use of minimum bubble point membranes for validation study.

"At least one of the filters used for bacterial retention testing should demonstrate a pretest water-wet integrity test result at or near the manufacturer's minimum integrity test specification."

"The pre-use integrity test values for production filters should be statistically based on the integrity test values of filters used for bacterial retention validation."

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"It is unclear how bacterial retention validation testing with filters in excess of the manufacturer's minimum integrity test specification validates use of filters at or near the minimum specification."

Manufacturing Production Limits and Trends

In evaluating the bubble point distribution for sterilizing-grade (0.22 µm) Durapore hydrophilic membrane, our data have shown that our process yields a mean bubble point value of 55.5 psig (3830 mbarg), and the minimum bubble point production limit is 50 psig (3450 mbarg). These data, which cover over 50,000 measurements, show that 99.9 % percent of membranes cast have a bubble point of greater than 50 psig (3450 mbarg).

To facilitate compliance with recent industry and regulatory initiatives in bacterial retention validation of sterilizing filtration, Millipore recommends the implementation of a minimum in-process bubble point specification of 50 psig (3450 mbarg). This bubble point specification is defined as the value at the low end of the filter membrane production limit. This value is the bubble point specification for all Durapore sterilizing grade membranes (figure 1). No filter device is released from manufacturing with bubble points below this value.

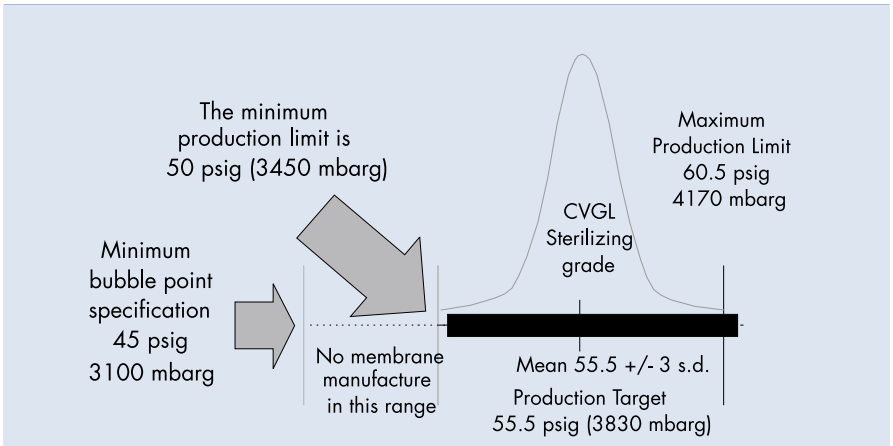


Figure 1: *Sterilizing grade Durapore membrane manufacturing limits and bubble point specification*

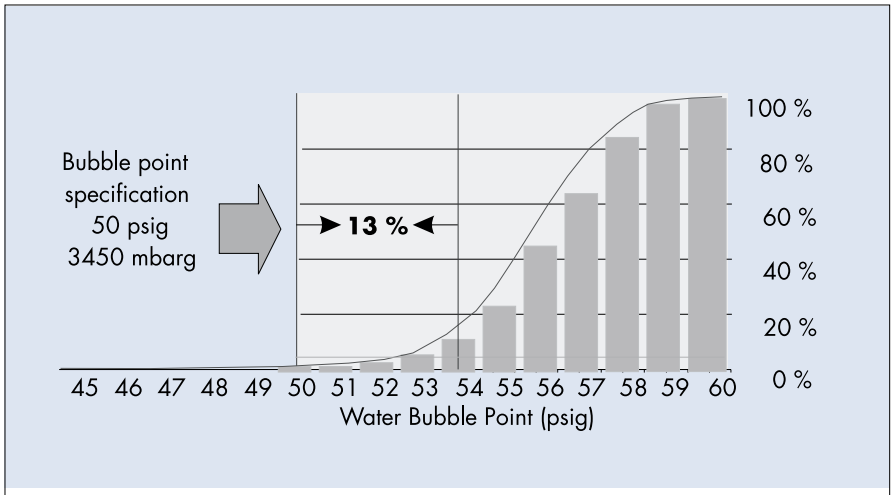


Figure 2*: Cumulative percent occurrence of bubble point values obtained from sterilizing-grade Durapore membrane lot release data.*

Bacterial Retention Validation Using Minimum Bubble Point Durapore Membranes

Membranes used for bacterial retention validation range between 50 and 54 psig (3450 and 3725 mbarg). In this sense, 50 to 54 psig (3450 to 3725 mbarg) can be said to be truly representative of low-end bubble point values from typical manufacturing, as this represents 13% of our membrane production. As such, these membranes are suitable candidates for bacterial retention validation (see figure 2).

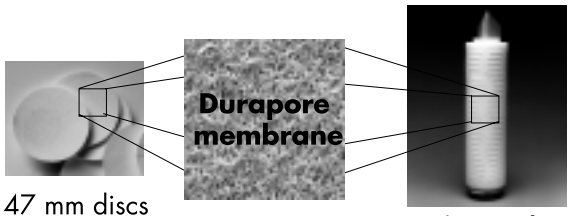
Challenging membranes with bubble point values ranging from 50 to 54 psig (3450 to 3725 mbarg) during bacterial retention validation studies supports the use of an in process specification of 50 psig (3450 mbarg).

Relationship Between Integrity Test Methods Used for Bacterial Retention Validation and Production Filters

Because sterilizing filtration is a critical step in aseptic processing, regulatory agencies require that specific validation protocols be conducted with actual drug product (2). The FDA requires product-specific bacterial retention testing to validate the consistent retention performance of sterilizing-grade filters in conditions simulating the most critical process parameters that may affect filter efficacy (3, 4).

Routine in-process integrity testing should clearly establish the similarity of production filters with those used in the product-specific validation study (see figure 4). The pre-use integrity test values for production filters should be based on the integrity test values of filters used for bacterial retention validation.

As illustrated in figure 3, Millipore is using identical membranes for bacterial retention validation and fabricating filter devices. Furthermore, the testing method used to assess production filters yields meaningful results in terms of the validation study performed under process-related conditions. Both production and validation filters are tested with the bubble point method, and membranes used for validation are representative of our minimum production limit.



47 mm discs
50 - 54 psig
3450 - 3725 mbarg

Production filter
BP ≥ 50 psig
BP ≥ 3450 mbarg

***Figure 3**: 47 mm membranes used for product-specific validation studies are representative of typical production membranes and yield bubble point values at or near the specification.*

Notification Process

At Millipore, we recognize the need for stable process materials in the pharmaceutical industry. Changes in a supplier's product can require revalidation of the pharmaceutical manufacturing process. However, continuous improvement efforts, change in raw materials by suppliers and improvements requested during customer audits may result in necessary changes to our products. A change notification process has been implemented to assure that changes to Millipore's products are communicated to our pharmaceutical customers.

Changes which affect product form, fit or function are communicated to our customers before implementation, so our customers can properly determine the impact the change may have on their processes. Change Notifications include detailed information to judge revalidation requirements and support change in our customers' documentation.

Millipore's change notification process is our way of balancing continuous improvement initiatives with the stability requirements of the pharmaceutical industry.

The customer change notification for the Durapore product bubble point change includes:

- Customer notification letter, as shown on the following pages, issued in May 1999
- Recommended review procedure, as shown on the following pages
- Implementation of change in December 1999
- Support documentation such as Validation Guides

Sample Notification Letter

May, 1999

Dear <Customer Name>

Reference: Change in Durapore minimum bubble point specification

The purpose of this letter is to notify you of Millipore's intention to increase the minimum bubble point specification for all sterilizing grade (0.22 µm) Durapore filtration products from 45psig (3100 mbarg) to 50psig (3450 mbarg). This change is being implemented to comply with current industry and regulatory practice related to the validation of minimum bubble point specifications for sterilizing grade filters. Please make sure the appropriate people in your organization receive a copy of this notification.

Implementation of the Change:

All 0.22 µm hydrophilic Durapore filters manufactured after December 1, 1999, will include Certificates of Quality that reflect the new minimum bubble point specification of 50 psig (3450 mbarg). Easy identification of the lot manufacturing date is facilitated by Millipore's Lot Numbering System (see enclosed description of Millipore's Lot Number System). The new Certificate of Quality will contain additional information concerning integrity testing in manufacturing and references to minimum bubble point specifications for water and methanol. For your reference a sample of the new Certificate of Quality has been enclosed with this letter.

The change in minimum bubble point specification will not take place until December 1, 1999, so that you will have enough time to implement the necessary changes in your quality systems and documentation. We recommend that all new processes be brought on line with the new minimum bubble point specification of 50 psig (3450 mbarg). Your documentation, training and performance of integrity testing for all existing processes should be changed to reflect the new minimum bubble point specification.

Reason for the Change:

Millipore is making this change in order to meet the most recent recommended validation practices outlined in the PDA guidance document; Technical Report No 26. This document indicates that membrane filters, that are at or near the minimum production limit for integrity test values, be used for the validation of bacterial retention. From a regulatory perspective, FDA investigators have interpreted this document to represent CGMP for the validation of aseptic filtration processes and require the use of filters that are at or near the minimum integrity test specification.

Scope of this Change:

This change notification affects all the following product types:

- Cartridge catalog numbers beginning with CVGL and CLGL
- Millidisk catalog numbers beginning with MCGL
- Millipak catalog numbers beginning with MPGL
- Opticap catalog numbers beginning with KVGL, KV03, KV06, KV19, KVSS, KVSC, KVSX
- Optiseal catalog numbers beginning with LAGL
- Cut Discs catalog numbers beginning with GVLP, GVWP, GVSP, GVHP293MP
- Special sterilizing grade products beginning with SI1, SJ1, SJ2, SN1or SN2
- Small area devices beginning with SLGV0, SLGVT, SLGVR, SLGVL, SVGV, SCGV, SFGV
- Membrane cut discs beginning with GVLP and GVWP
- Centrifugal Filters beginning with UFC30GV, UFC40GV
- Minitan Plates beginning with GVLP and Multiscreen plates beginning with MAGV

Background Information:

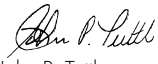
No changes have been made to the membrane or filter devices in either how they are manufactured or tested. All performance specifications (flow rate, stress testing and integrity) and product attributes (materials of construction, extractables and endotoxin specifications) remain unchanged.

A review of historical bubble point trends for both membranes and devices shows that 99.9% of production over the last 5 years has been in the 50 to 60 psig range. In terms of production capability this represents a C_{pk} of >1.1 and as such is considered a robust process.

The introduction of a higher bubble point specification represents a "paper" change only. We are simply aligning the minimum bubble point specification with the actual minimum bubble point values our manufacturing processes have produced over the past five years. In accordance with Millipore's Change Notification Policy this is a Minor Change. Product form, fit or function is not affected by this change. This notwithstanding, we recognize the practical implications of such a specification change. Millipore intends to phase in this specification change by supporting both the old and the new minimum bubble point specifications for a period of 6 months to allow for the necessary changes to be made to your quality systems and documentation. I have enclosed a checklist that will help make the transition to the new bubble point specification as smooth as possible. Your Millipore application specialist is also available to help you with the transition. Please be aware that until December 1, 1999, Certificates of Quality will continue to reference a minimum bubble point specification of ≥45 psig (3100 mbarg).

We strongly believe that this course of action is in the best interest of our customers. Millipore values you as a customer and we want to make sure this change in minimum bubble point specification can be implemented in an objective and straightforward manner. If you have any questions, please do not hesitate to contact a Millipore Technical Service representative or your Millipore application specialist at 1-800-645-5476.

Sincerely



John P. Tuttle
Quality Systems, BioProcess Division, Millipore Corporation

Action Item Checklist

1. **Pending Regulatory Submissions**
   Review and ensure that all references to in-process integrity test values reflect the new minimum water bubble point specification of 50psig (3450mbarg). This should include ensuring that any references to product bubble point ratios are calculated from the new minimum water bubble point specification.

2. **Existing Processes**
   Review process integrity test (bubble point) history for all existing processes. This review should be conducted for consistency of methodology and to ascertain if routine testing yields a water bubble point consistently less than 50psig (3450mbarg). In these situations, product bubble point ratios or alternative integrity methods will need to be considered. Your local Millipore application specialist will be a valuable resource in reviewing these options.

3. **Bubble Point Ratio**
   If you have determined a product versus water bubble point ratio which is used to determine an acceptable bubble point for a post use integrity test, you will need to recalculate the minimum acceptable bubble point. Multiply the bubble point ratio by 50 to determine your minimum acceptable post use bubble point. If you require any assistance with the formal documentation of an acceptable product bubble point, please contact your application specialist.

4. **Documentation**
   Identify and change (using approved change control procedures) all manufacturing documents that reference water or product bubble point specifications. Documents that should be reviewed include process specifications, standard operating procedures, test methods, batch or lot manufacturing records, and manufacturing "Job Sheets" or Tickets" filled out by technicians or operators.

5. **Automated Integrity Testers**
   Identify all automated integrity testers, identify all bubble point programs and change them (using approved change control procedures) to reflect the new minimum bubble point specification. Both water and product bubble points need to be changed.

6. **Incoming inspection**
   Ensure that purchasing and incoming inspection are informed of these changes especially if there is a policy in place to check Certificate of Quality information against an expected template.

7. **Inventory Control**
   After December 1, 1999, all new product will reference 50psig (3450mbarg) as our QC lot release bubble point test. There will be, in both Millipore and your inventory, product with certificates that reference 45psig (3100mbarg) as the QC lot release bubble point test. It is entirely possible that for a few months after December 1, 1999, you will receive older and newer product. Your documentation and quality systems will need to be able to accept and use both types of product. This presents no practical problem as there has been no material change to the product or it's performance specifications. For this reason Millipore does not intend to accept returns. Please ensure that your systems can cope with this eventuality.

Common Questions

Does this specification change require Revalidation?

The critical question is "what kind of revalidation work could be required following a documentation change that has no impact on the actual product that you receive from us?".

We have come to the conclusion that for the large majority of cases, revalidation should not be necessary in the following areas:

- *Bacterial retention validation*. In fact, the specification change will tend to help in the case where a validation study had been performed using 50-54 psig membrane disks. In this case, the new specification will bring this study into closer alignment with the new regulatory trend and could actually prevent one from having to redo a validation, should the original study be revisited by the FDA in the future. It is possible that one would find it prudent to revalidate bacterial retention if the original study did not include a disk of 54 psig or below. In this case, it is important to note that this revalidation would be driven by a need to revalidate under the new regulatory trend, and not because of our specification change. In other words, our need to change the specification and their need to revalidate would be motivated by this same regulatory trend.
- *Extractables*: It is very difficult to conceive of a situation in which this paper change could cause a need to revalidate for extractables.
- *Process validation/stability studies/etc*. It is very difficult to conceive of a situation in which this paper change could cause a need for revalidation of the process.

Theoretically, the only reason we can conceive of that one would need to revalidate due to the specification change is:

- If the specification of 45 psig were used in a validation study to prove that the filter were integral following some manipulation (e.g., autoclave sterilization cycle validation or chemical compatibility validation).
- If the actual data obtained in the study contained BP values between 45 and 49. In this case, the appearance could be that those devices might be considered non-integral vis a vis the new specification.

In actuality, we anticipate that this type of occurrence will be very infrequent because of our historical bubble point ranges. Of course, our experts can help in the review of data that people might be concerned about. However, the question of whether to revalidate is one that is ultimately up to the customer. Moreover, we cannot be expected to correctly anticipate FDA's reaction to every individual case.

How do I manage specific bubble point ratio studies made in the past?

The ratios themselves remain unchanged. However, the minimum bubble point specification which gets multiplied by that ratio has been increased from 45 psig to 50 psig.

You tell me your manufacturing has not changed, do you have bubble point trend data to support this?

Yes, figures 1 and 2 contain the data that shows the bubble point trends for our 0.22um hydrophilic membrane and devices over the last 5 years.

This data shows that 99.9% of our product released against our old bubble point specification of 45 psi would in fact have passed the increased specification of 50 psi.

Is the diffusion rate going to change and therefore the specification? If not why not?

Remember the membrane has not changed. As the actual bubble point of the membrane as supplied has not changed, and there have been no changes to membrane porosity and thickness it stands to reason that there will be no change in the diffusion rate or in the specification either.

What does the FDA think?

We have presented our data and our validation approach regarding minimum bubble point in discussions on sterile filtration with the FDA. As expected, we received no approval but at the same time were not chastised for the approach. We have applied our best knowledge of membranes and filtration in trying to find a meaningful way to support the FDA's intent of improving the practice of bacterial retention validation. We have also written responses to FDA observations and have not received any adverse comments to date.

How does this change affect NDAs we have submitted to the FDA? What should I do?

The FDA reviewer may ask a question concerning minimum bubble point bacterial retention citing a 45 psi specification as being too far removed from the value of the membranes used in the validation test. The response to this concern should be to inform them of your intent to move the minimum specification to 50 psi to be in line with Millipore's recent specification change.

How can you support the use of a 50 to 54 psi bubble point disk in validation as being representative of your minimum specification of 50 psi?

The validation requirement for microbial retention is that disks used are at or near the minimum specification. The 50 to 54 psi range is within 8% of the minimum specification and therefore meets this validation requirement.

References

1 - PDA Journal of Parenteral Science and Technology, Vol. 52, No. S1. Technical Report No. 26. "Sterilizing Filtration of Liquids". March 1998. Section 6.2, point 2.

2 - FDA Guideline on Sterile Drug Products Produced by Aseptic Processing. June 1987.

3 - Leahy, T.J. and Sullivan, M.J., "Validation of bacterial retention capabilities of membrane filters," Pharm. Technol., Vol. 2, 65, (1978).

4 - Levy, R.V., "Microbial retention testing of sterilizing-grade filters with final parenteral products," Paper presented at PDA Annual Meeting, October, 1998.

To Place an Order or Receive Technical Assistance

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