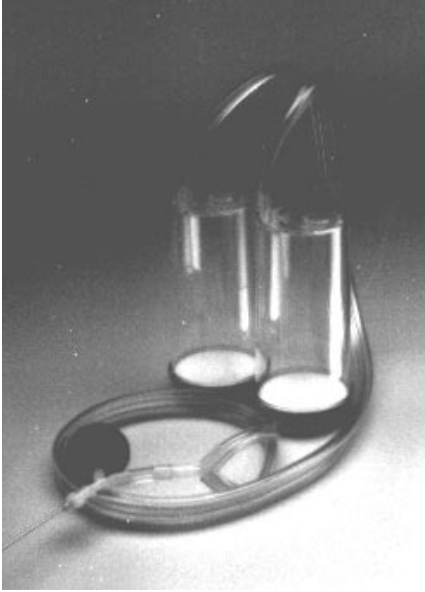


TECHNICAL BRIEF

The Effect of Vaporous Hydrogen Peroxide on Steritest™ Sterility Testing Devices

A Joint Study Conducted
By Millipore and a
BioPharmaceutical Customer





I. Introduction

Closed, disposable Steritest sterility test devices reduce the risk of false positives during the sterility testing of pharmaceuticals. To further reduce the risk of false positives, some manufacturers use the devices inside an isolator. Typically, the filtration devices are placed in the isolator while the isolator is decontaminated using sterilization gases.

In this study, pre-sterilized Steritest devices were exposed to two 90-minute vaporous hydrogen peroxide (VHP) cycles. This design simulates one particular sterilization scenario in which filtration devices are placed inside an isolator prior to a sterility test and are treated with VHP. The devices are not used during the sterility testing and remain in the isolator until the next test day. Prior to the second sterility test, the isolator (and the Steritest devices) is treated with VHP again.

The purpose of this study is to answer the following questions:

- Does exposure to VHP affect device performance?
- If there is an effect, are different membrane filter materials (PVDF and MCE) affected differently?
- Is device performance affected over time?

Different tests were selected and executed on Steritest units before and after contact with VHP to answer the questions posed in this study:

- Membrane bubble point test was conducted to ensure that neither the membrane nor device was damaged.
- A panel of five microorganisms was chosen for bacteriostasis/fungistasis testing in FTG and TSB media. Two strains of *Staphylococcus* were chosen due to their particularly high sensitivity to VHP. Bacteriostasis/fungistasis tests were performed on Steritest units after two rinsing steps with 100 mL of Fluid A per canister. Negative media controls were also included.
- Gravimetric extractables tests (non-volatile residues, FTIR) were conducted after extraction in water (24-hour soak). NVR was used for quantitative analysis and FTIR for qualitative identification of extractables.

The results are only valid for the conditions set for this study. Since isolators, isolator configurations, isolator contents, and sterilization protocols may vary, isolator users should validate their test independently.

II. VHP Sterilization Cycle Parameters

The tested Steritest units were exposed to two consecutive 90-minute VHP cycles. The VHP treatments were performed on-site with the client's isolator. The isolator characteristics and the details of these cycles are shown below.

Isolator volume:	22 ft ² (0.6 m ²)
Dehumidify air set:	22 scfm (623 L/min)
Dehumidify to:	2.3 mg/L
Dehumidify time:	5 min
Preheater temperature set:	90 °C (194 °F)
Vaporizer temperature set:	100 °C (212 °F)
Condition air set:	16 scfm (453 L/min)
Condition injection rate:	4 g/min
Sterilize air set:	16 scfm (453 L/min)
Sterilize injection rate:	2.5 g/min
Sterilize time:	90 min
Aerate air set:	22 scfm (623 L/min)
Aerate time:	4 hr
Blower set to run after aerate time out:	12 hr

III. Experimental Design

The study included two phases. In Phase 1, a full factorial, two factor (two level), balanced block experiment was performed to evaluate the bubble point of the membranes in the Steritest canisters. The bubble point test is the most sensitive way to measure membrane performance.

Based on the results of Phase 1, a test design was established for Phase 2, which was comprised of bacteriostasis/fungistasis testing and gravimetric extractables evaluation.

PHASE 1 (Figure 1)

Factor 1: two membrane polymers (two lot numbers for each Steritest type)

- MCE (Mixed Cellulose Esters membrane used in Steritest HA)
- PVDF (Polyvinylidene Fluoride membrane used in Steritest HV)

Factor 2: two time points

- Initial study
- 7 months later

Trials done on:

- Steritest pre-VHP sterilization cycles.
- Steritest post-VHP sterilization cycles
 - Two different VHP runs A and B (we assumed there was variability between VHP loads, thus all factors and levels were accommodated within the test block).
 - There was a one-to-one comparison with the control (untreated) samples.

Note: the experiment included a total of 32 canisters or 16 Steritest canister sets (8 PVDF sets and 8 MCE sets).

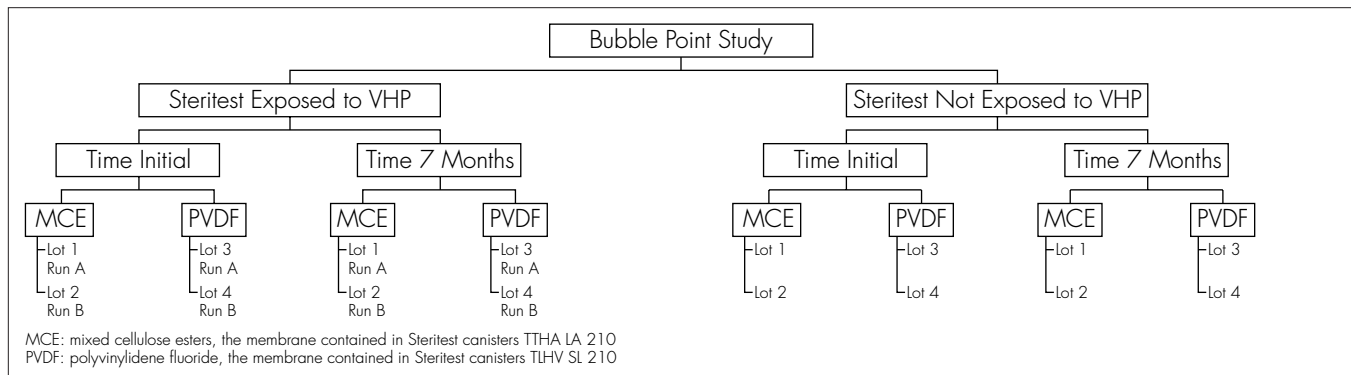


Figure 1. PHASE 1. Bubble point test. The tree diagram displays the full factorial, two factor, two level design of the study. The treatment was two 90-minute cycles of VHP.

PHASE 2 (Figure 2)

Factor 1: two membrane polymers (four lot numbers for each Steritest type)

- MCE (Mixed Cellulose Esters membrane used in Steritest HA)
- PVDF (Polyvinylidene Fluoride membrane used in Steritest HV)

Factor 2: two time points

- Initial study
- 7 months later

Trials done:

- Steritest pre-VHP sterilization cycles.
- Steritest post-VHP sterilization cycles
 - 3 replicates.
 - 4 different VHP runs (we assumed there was variability between VHP loads).
 - There was a one-to-one comparison with the control (untreated) samples.

Note: Phase 2 required 48 canister sets with MCE membrane from four different lot numbers and 48 canisters sets with PVDF membrane from four different lot numbers.

To ensure that Steritest canisters from the three replicates were not exposed to the same VHP cycle, the three bacteriostasis/fungistasis replicates were divided into four VHP runs (Table 1).

Each grouping (for example, Replicate 1, MCE, VHP Run 1) included five Steritest canister sets plus one negative control canister set.

Table 1. Sterilization Plan

	Time Point			
	0 Months		7 Months	
	MCE	PVDF	MCE	PVDF
Replicate 1	VHP run 1	VHP run 1	VHP run 1	VHP run 2
Replicate 2	VHP run 3	VHP run 2	VHP run 2	VHP run 3
Replicate 3	VHP run 4	VHP run 3	VHP run 4	VHP run 4

Extractables study

Materials used for this study:

- 1 control with water.
- 1 Steritest unit TTHALA210 (MCE membrane) pre-VHP sterilization.
- 1 Steritest unit TTHALA210 (MCE membrane) post-VHP sterilization.
- 1 Steritest unit TLHVSL210 (PVDF membrane) pre-VHP sterilization.
- 1 Steritest unit TLHVSL210 (PVDF membrane) post-VHP sterilization.

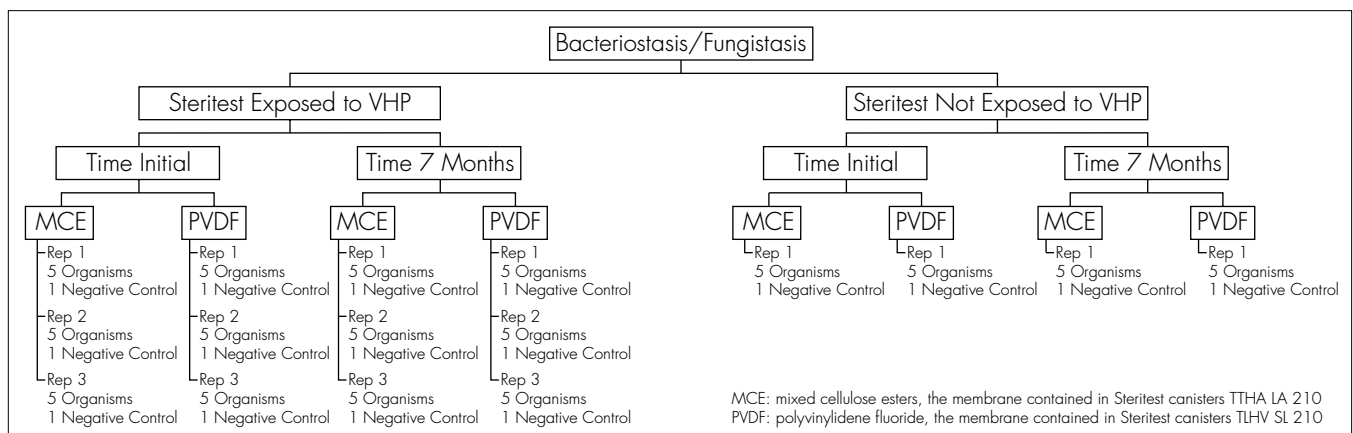


Figure 2. PHASE 2. Bacteriostasis/fungistasis test design. The tree diagram displays the full factorial, two factor, two level design of the study. The treatment was two 90-minute cycles of VHP.

IV. Material and Methods

PHASE 1

Steritest HA,

Millipore cat. no. TTHA LA2 10

Lot 1 R5JM60636

Lot 2 R5MM60824

Steritest for Solvents,

Millipore cat. no. TLHV SL2 10

Lot 3 F5HM81611

Lot 4 F5KM81550

Bubble Point Test (Figure 3)

Purpose: to measure the integrity of Steritest sterility test devices using "bubble point" as the measurement criterion.

Equipment: Automatic Integrity Tester, Integritest® II (Millipore cat. no. XEIT 110 11)

PHASE 2

Bacteriostasis/Fungistasis Test

Purpose: to evaluate the presence or absence of inhibitory residuals due to VHP treatment.

In this test, each canister was rinsed twice with 100 mL of Fluid A before the filtration of the last 100 mL Fluid A with the test microorganism. Then, the growth medium was added.

Steritest units used for this study:

Steritest HA,

Millipore # TTHA LA 210

Lot R5JM60626

Lot R5MM60824

Lot R6CM68235

Lot R6EM13545

Steritest for Solvents,

Millipore # TLHV SL 210

Lot F6AM81551

Lot F5NM81788

Lot F5HM81611

Lot F5KM81550

Test microorganisms:

Bacillus subtilis (ATCC® 6633)

Candida albicans (ATCC 10231)

Clostridium sporogenes (ATCC 11437)

Staphylococcus epidermidis (ATCC 12228)

Staphylococcus aureus (ATCC 6538)

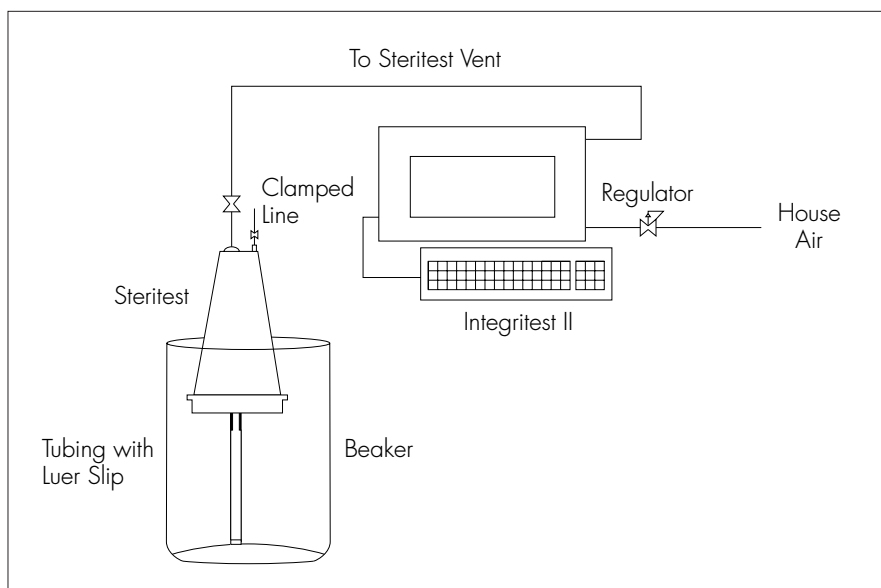


Figure 3. Steritest Bubble Point Test Using an Integritest® II Automatic Integrity Tester

Acceptance Criteria:

- Negative controls shall demonstrate no growth as determined visually after incubation for 14 days.
- Inoculum concentration of each test microorganism delivered to the specified Steritest canister shall be between 10 and 100 cfu (cf. Plate count results).
- Positive controls shall demonstrate growth of the specified test microorganism (USP24: growth within 5 days for bacteria, yeast, and molds).
- Inoculated test canisters shall demonstrate growth that is visually comparable to the positive control.

Gravimetric Extractables

Purpose: the weight of extractables and the HPLC and FTIR profiles for Steritest sterility test devices have been determined after soaking at ambient temperature (20 °C) in ASTM type 1 reagent-grade water for 24 hours.

Steritest units used for this study:

Steritest HA,

Millipore # TTHA LA 210

Lot R5JM60626 x 2

Steritest for Solvents,

Millipore # TLHV SL 210

Lot F5HM81611 x 2

Equipment: Drying oven capable of 80 °C ± 5 °C

V. Results

Bubble Point Test

All of the 32 canisters met the acceptance criteria for bubble point. The Initial bubble point range was:

- PVDF: 24.1 to 26.3
- MCE: 31.1 to 35.3

There is no statistical difference between VHP-treated versus non-VHP-treated devices for bubble point at T_{initial} or $T_{7\text{Months}}$.

Bacteriostasis/Fungistasis Test

Growth of all test microorganisms were as expected. No static or cidal effects were observed. All canisters met the acceptance criteria for the tests being conducted.

A) Bacteriostasis/Fungistasis Tests at T_{Initial}

Table II. Time_{Initial} Plate Count Results

Microorganism	Microorganism Lot Information	Rep 1 (cfu)	Rep 2 (cfu)	Mean	St. Dev.
<i>C. albicans</i>	Pass # 4, 6.9 x 10 ⁷ cfu/mL Lot MB-121-111	40	50	45	7.1
<i>S. aureus</i>	Pass # 5, 2.0 x 10 ⁹ cfu/mL Lot MB-24147-8	43	22	33	14.8
<i>S. epidermidis</i>	Pass # 3, 3.1 x 10 ⁸ cfu/mL Lot RJK-8318-101	27	27	27	0.0
<i>B. subtilis</i>	Pass # 5, 3.1 x 10 ⁷ cfu/mL Lot MB-121-88	59	73	66	9.9
<i>C. sporogenes</i>	Pass # 3, 4.8 x 10 ⁴ cfu/mL Lot MB-121-109	54	65	60	7.8

Table III. Time_{Initial} Results for *Staphylococcus epidermidis*

Membrane	Lot	VHP Cycle	TSB(hours)	FTM (hours)
MCE	R5JM60626	1	+ 48-120*	+ 24
MCE	R6EM13545	3	+ 48-120*	+ 48
MCE	R6CM68235	4	+ 48	+ 24
PVDF	F5NM81788	1	+ 48-120*	+ 24
PVDF	F6AM81551	2	+ 48-120*	+ 24
PVDF	F5KM81550	3	+ 48-120*	+ 24
MCE + Control	R6EM13545	No VHP Cycle	+ 48-120*	+ 48
PVDF + Control	F5KM81550	No VHP Cycle	+ 48-120*	+ 48

* Result was negative on a Friday and positive on a Monday. The units were not examined over the weekend.

Table IV. Time_{Initial} Results for *Staphylococcus aureus*

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R5JM60626	1	+ 48-120*	+ 24 hr
MCE	R6EM13545	3	+ 48-120*	+ 24 hr
MCE	R5MM60824	4	+ 48-120*	+ 24 hr
PVDF	F6AM81551	1	+ 48-120*	+ 24 hr
PVDF	F5NM81788	2	+ 48	+ 24 hr
PVDF	F5KM81550	3	+ 48-120*	+ 24 hr
MCE + Control	R6CM68235	No VHP Cycle	+ 48	+ 24 hr
PVDF + Control	F5NM81788	No VHP Cycle	+ 48	+ 24 hr

* Result was negative on a Friday and positive on a Monday. The units were not examined over the weekend.

Table V. Time_{Initial} Results for *Candida albicans*

Membrane	Lot	VHP Cycle	TSB (hours)
MCE	R5MM60824	1	+ 48
MCE	R5JM60626	3	+ 48
MCE	R6CM68235	4	+ 48
PVDF	F5KM81550	1	*
PVDF	F5HM81611	2	+ 48
PVDF	F6AM81551	3	+ 48
MCE + Control	R6CM68235	No VHP Cycle	+ 48
PVDF + Control	F5NM81788	No VHP Cycle	+ 48

* Test was not performed. The tubing was accidentally damaged prior to the test.

Table VI. Time_{Initial} Results for *Bacillus subtilis*

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R6EM13545	1	+ 24-96 hr*	+ 24 hr
MCE	R5MM60824	3	+ 24-96 hr*	+ 24 hr
MCE	R6EM13545	4	+ 24-96 hr*	+ 24 hr
PVDF	F5HM81611	1	+ 24-96 hr*	+ 24 hr
PVDF	F5KM81550	2	+ 24-96 hr*	+ 24 hr
PVDF	F5NM81788	3	+ 24-96 hr*	+ 24 hr
MCE + Control	R6CM68235	No VHP Cycle	+ 24-96 hr*	+ 24 hr
PVDF + Control	F5NM81788	No VHP Cycle	+ 24-96 hr*	+ 24 hr

* Result was negative on a Friday and positive on a Monday. The units were not examined over the weekend.

Table VII. Time_{Initial} Results for *Clostridium sporogenes*

Membrane	Lot	VHP Cycle	TSB (hours)*
MCE	R6CM68235	1	+ 24 hr
MCE	R5MM60824	3	+ 24 hr
MCE	R5JM60626	4	+ 24 hr
PVDF	F6AM81551	1	+ 24 hr
PVDF	F5KM81550	2	+ 24 hr
PVDF	F5HM81611	3	+ 24 hr
MCE + Control	R6CM68235	No VHP Cycle	+ 24 hr
PVDF + Control	F6AM81551	No VHP Cycle	+ 24 hr

* Because *Clostridium sporogenes* is an anaerobe, the test was performed in Fluid Thioglycollate Medium only.

Table VIII. Time_{Initial} Negative Controls

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R5JM60626	No VHP Cycle	NG*	NG
MCE	R6CM68235	1	NG	NG
MCE	R5JM60626	3	NG	NG
MCE	R6CM68235	4	NG	NG
PVDF	F5NM81788	No VHP Cycle	NG	NG
PVDF	F5NM81788	1	NG	NG
PVDF	F5HM81611	2	NG	NG
PVDF	F6AM81551	3	NG	NG
FTM Medium Negative Control	2311	No VHP Cycle	NG	NG
TSB Medium Negative Control	2315	No VHP Cycle	NG	NG

*NG denotes no growth was observed after 14 days of incubation at the appropriate temperature for the medium being tested.

B) Bacteriostasis/Fungistasis Tests at T_{7Months}

Table IX. Time_{7 Months} Plate Count Results

Microorganism	Microorganism Lot Information	Rep 1 (cfu)	Rep 2 (cfu)	Mean	St. Dev.
<i>C. albicans</i>	Pass # 3, 2.2 x 10 ⁸ cfu/mL Lot MB-24147-49	43	51	47	5.7
<i>S. aureus</i>	Pass # 4, 8.1 x 10 ⁴ cfu/mL Lot WG-24099-47	43	45	44	1.4
<i>S. epidermidis</i>	Pass # 3, 5.0 x 10 ³ cfu/mL Lot WG-112-56-58	72	59	66	9.2
<i>B. subtilis</i>	Pass # 4, 1.3 x 10 ⁸ cfu/mL Lot MB-24147-48	36	56	46	14.1
<i>C. sporogenes</i>	Pass # 4, 6.9 x 10 ⁶ cfu/mL Lot MB-24147-25	75	84	80	6.4

Table X. Time_{7 Months} Results for *Staphylococcus epidermidis*

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R6CM68235	1	+ 72-144*	+ 24
MCE	R5MM60824	2	+ 72-144*	+ 24
MCE	R6CM68235	4	+ 72-144*	+ 24
PVDF	F5HM81611	2	+ 72-144*	+ 24
PVDF	F5HM81611	3	+ 72-144*	+ 24
PVDF	F5NM81788	4	+ 72-144*	+ 24
MCE + Control	R6EM13545	No VHP Cycle	+ 72-144*	+ 24
PVDF + Control	F5NM81788	No VHP Cycle	+ 72-144*	+ 24

* Result was negative on a Friday and positive on a Monday. The units were not examined over the weekend.

Table XI. Time_{7 Months} Results for *Staphylococcus aureus*

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R5MM60824	1	+ 48	+ 24 hr
MCE	R6CM68235	2	+ 48	+ 24 hr
MCE	R5MM60824	4	+ 48	+ 24 hr
PVDF	F5HM81611	2	+ 48	+ 24 hr
PVDF	F5NM81788	3	+ 48	+ 24 hr
PVDF	F6AM81551	4	+ 48	+ 24 hr
MCE + Control	R6CM68235	No VHP Cycle	+ 48	+ 24 hr
PVDF + Control	F5NM81788	No VHP Cycle	+ 48	+ 24 hr

Table XII. Time_{7 Months} Results for *Candida albicans*

Membrane	Lot	VHP Cycle	TSB (hours)
MCE	R6EM13545	1	+ 48
MCE	R6CM68235	2	+ 48
MCE	R6CM68235	4	+ 48
PVDF	F5NM81788	2	+ 48
PVDF	F5KM91550	3	+ 48
PVDF	F5NM81788	4	+ 48
MCE + Control	R6CM68235	No VHP Cycle	+ 48
PVDF + Control	F5HM81611	No VHP Cycle	+ 48

Table XIII. Time_{7 Months} Results for *Bacillus subtilis*

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R6CM68235	1	+ 48 hr	+ 24 hr
MCE	R5JM60626	2	+ 48 hr	+ 24 hr
MCE	R6EM13545	4	+ 48 hr	+ 24 hr
PVDF	F6AM81551	2	+ 48 hr	+ 24 hr
PVDF	F6AM81551	3	+ 48 hr	+ 24 hr
PVDF	F5KM81550	4	+ 48 hr	+ 24 hr
MCE + Control	F5HM81611	No VHP Cycle	+ 48 hr	+ 24 hr
PVDF + Control	F6AM81551	No VHP Cycle	+ 48 hr	+ 24 hr

Table XIV. Time_{7 Months} Results for *Clostridium sporogenes*

Membrane	Lot	VHP Cycle	TSB (hours)*
MCE	R5JM60626	1	+ 24 hr
MCE	R6EM13545	2	+ 24 hr
MCE	R5JM60626	4	+ 24 hr
PVDF	F5NM81788	2	+ 24 hr
PVDF	F5NM81788	3	+ 24 hr
PVDF	F5NM81788	4	+ 24 hr
MCE + Control	R6CM68235	No VHP Cycle	+ 24 hr
PVDF + Control	F5NM81788	No VHP Cycle	+ 24 hr

* Because *Clostridium sporogenes* is an anaerobe, the test was performed in Fluid Thioglycollate Medium only.

Table XV. Time_{7 Months} Negative Controls

Membrane	Lot	VHP Cycle	TSB (hours)	FTM (hours)
MCE	R5MM60824	No VHP Cycle	NG*	NG
MCE	R6EM13545	1	NG	NG
MCE	R5MM60824	2	NG	NG
MCE	R6CM68235	4	NG	NG
PVDF	F6AM81551	No VHP Cycle	NG	NG
PVDF	F5KM91550	2	NG	NG
PVDF	F5NM81788	3	NG	NG
PVDF	F5HM81611	4	NG	NG
TSB Medium Negative Control	2315	No VHP Cycle	NG	NG
FTM Medium Negative Control	2311	No VHP Cycle	NG	NG

*NG denotes no growth was observed after 14 days of incubation at the appropriate temperature for the medium being tested.

Gravimetric Extractable Analysis

The water extraction study showed a significant difference in the amount of non-volatile residue for the VHP-treated Steritest for Solvents Canisters with PVDF membrane as compared to the other values. The IR spectra of all the extractions suggest the presence of inorganic materials such as salts. However, nothing unusual could be identified.

Table XVI. Non-Volatile Residue Gravimetric Extractables Results

Sample ID	Steritest Catalogue Number	Steritest Lot Number	Gross NVR Residue Corrected for Vol. Analyzed (mg/ml)	Residue per Device Adjusted for Extraction Vol. (mg)
Control H2O	N/A	N/A	0.0000	—
MCE (VHP)	TTHALA210	R5JM60626	0.0044	1.1664
MCE (no VHP)	TTHALA210	R5JM60626	0.0049	1.3211
PVDF (VHP)	TLHVSL210	F5HM81611	0.0851	22.6208
PVDF (no VHP)	TLHVSL210	F5HM81611	0.0146	3.8532

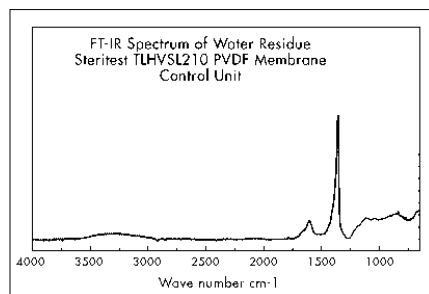


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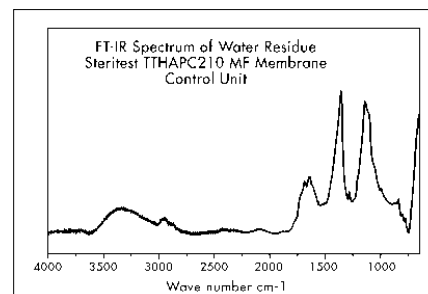


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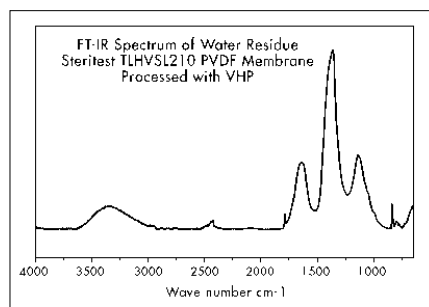


Figure 5.

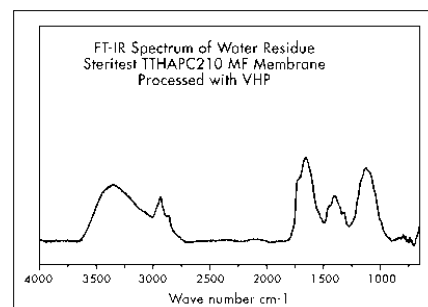


Figure 7.

Figures 4-7. FTIR Spectra of Untreated and VHP-Treated Steritest PVDF and MCE Devices.

VI. Conclusions

- It appears that the primary function of Steritest canisters is not impaired by two 90-minute VHP cycles.
- Bubble point results suggest no membrane structural and performance changes over time due to VHP treatment.
- Bacteriostasis/fungistasis tests done with standard microorganisms described in USP 24 and with *Staphylococcus epidermidis* (ATCC12228) sensitive to VHP show no evidence of inhibitory residuals over time after rinsing the membrane twice with 100 mL Fluid A per canister.

- Qualitative extractable analysis did not identify unusual chemical components. No correlation was possible between the amount of non-volatile residues and contact of the Steritest with VHP.
- These conclusions are only valid for the conditions evaluated in this study. Each isolator must be validated independently because each isolator's configuration, contents, and sterilization cycle protocols vary.

In the "normal" conditions used in this study, repeated exposure to isolator sterilization cycles did not adversely affect the characteristics of the Steritest devices that are pertinent for a sterility test.

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