

FilterTEF 0.2 micron

Validation Guide



SISTEMI DI FILTRAZIONE

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➤General information filter cartridges FilterTEF

In a pharmaceutical production process, filtration is a very important step. It guarantees the depletion of any particles or microbial contaminants from the drug being processed. The filtration process must meet high and well defined quality standards.

Filter cartridges validation is mandatory to ensure purity, security and effectiveness to a pharmaceutical product.

The purpose of this document is to supply with useful information every End User of FilterTEF filter cartridges. 0.2 µm rated, operating in pharmaceutical applications. The document provides all references about test methods used and results obtained confirming cartridges conformity to the applicable requirements.

FilterTEF filter cartridges 0.2 micron rated are designed and manufactured for use in production of sterile liquids in pharmaceutical industry. Materials used for the assembly of the cartridges, both the Nylon membrane and the Polypropylene polymer used for the hardware supports, had been selected for the specific application meeting the current regulations.

All the assembling steps are carried out by means of thermal bonding processes, without adding adhesive material. *FilterTEF* are made in controlled contamination clean room and tested prior shipment by QA & QC IPM labs, following internal procedures, in order to meet the reference values set.

A wide range of product configurations are available. IPM Filters assigns a unique ID number to each product specific to its source of supply to enable traceability in combination with its lot number. The identification of the *FilterTEF* filter cartridges are made using the following part number guide:

TEF	2	10	002	S	I	PH
	Configuration adapter	Lenght	Filtration rating	Gaskets/ O-rings	Insert	Version
Product identification TEF	2= bayonet 2.226/flat 3= 2.222/flat 5= bayonet 2.222/fin 7= bayonet 2.226/fin 8= 2.222/fin	10=10" 20=20" 30=30" 40=40"	002= 0.2 µm	S= silicone V= Viton® X= other** ** pl.se contact IPM	I= SS insert* 0= no SS insert * use SS insert when you steam sterilize the filter	PH= Pharma version
	J= Junior cartridge	02=2.5" 05=5.0"				

Should you need any more info please contact IPM technical support tel. +39 039 21 45 244 or visit the site www.ipmfilters.com

► Filter cartridges FilterTEF 0,2 µm-technical characteristics

Materials of construction				
Membrane	Polietersulfone (PTFE)			
Support layers	Polypropylene (PP)			
Cartridge supports	Polypropylene (PP)			
O-rings	Silicone			
Technical characteristics				
Filtration area	0.78 m² (10'' module)			
Pores size	0.2 µm			
Length	Cartridges are available with the following dimensions: 5'' JUNIOR (125 mm), 10'' (250 mm), 20'' (500 mm), 30'' (750 mm)			
Retention characteristics				
Bacterial retention	Retention of 10 ⁷ CFU/cm ² Brevundimonas diminuta (ATCC 19146), as per ASTM F838-05.			
Mechanical characteristics				
Hydraulic Stress Resistance	FilterTEF filter cartridges 0,2 µm rated showed to retain their diffusion and integrity characteristics after the following hydraulic stress tests			
	Water Pressure (bar)	N° of strokes	Water temperature (°C)	Flow direction
	5.0	50	20±5	Forward
	2.0	50	20±5	Reverse
Thermal Stress Resistance	FilterTEF filter cartridges 0,2 µm rated showed to retain their diffusion and integrity characteristics after the following thermal stress tests			
	Temperature Test (°C)	Pressure Test (bar)	Cycle Time ¹ (hours)	N° of cycles (in autoclave)
	121	1.15	1	50
Estractables				
Estractables	FilterTEF 0.2 filter cartridges meet USP<661>.			
Conformity of materials to the rules for food contact	The materials used to produce the FilterTEF 0,2 µm cartridge filters were confirmed to be compliant with the requirements for food contact prescribed in Reg. N° 1935/2004/EEC and meet the FDA Indirect Food Additive requirements cited in 21 CFR 177 – 182.			
Biological reactivity				
Toxicity of materials	All the materials of the FilterTEF 0,2 µm filter cartridges meet the requirements of USP<87> ("Biological Reactivity Test in vitro for Class VI Plastics") and USP<88> ("Biological Reactivity Test in vivo for Class VI Plastics – Safety Test").			
Release of particles and/or Endotoxins				
Bacterial endotoxins	< 0.25 EU/mL of aqueous extract as per USP<85>.			
Non-fibre releasing	FilterTEF 0.2 µm filter cartridges satisfy the requirements as per USP<788>			

¹ Total time considering warming up time of 15 minutes; 30 minutes at test temperature and 15 minutes for cooling down to ambient temperature.

► Bacteria Removal efficiency

Regulator Authorities FDA and EMA, set the rule to demonstrate the sterilizing action of a filter before to start to use it in pharmaceutical applications. Therefore, the sterilizing grade of a filter cannot be set only by the rating of pores dimension.

In order to consider a filter of sterilizing grade it must be submitted to a process simulation challenging it by a bacterial suspension of *Brevundimonas diminuta* ATCC 1946 at the concentration of not less than 10^7 CFU/cm². The downstream fluid must be sterile.

This must be done both for the qualification of the membrane, using 47 mm discs, and for the qualification of the production process of cartridges and / or filter capsules.

The correlation between the microbial retention and the non-destructive integrity test is another very important aspect of the validation of a pharmaceutical grade filter cartridge.

The Regulator Authorities require a procedure to control the filter both prior and after the use.

According to the ASTM F838-05 method, the tests demonstrate the ability of membranes, used to produce FilterTEF, to fully retain a *Brevundimonas diminuta* bacterial charge of 10^7 CFU/cm².

Hereinafter are reported the Challenge tests results made on a 10" FilterTEF filter cartridges 0.2 µm rated, to validate its process of production.

You can also find the correlation between the retention and the diffusion test.

This correlation is important to set the maximum diffusion flow acceptance limit to guarantee that the filter will produce a sterile effluent.



► Filter cartridge type TEF 7 10 002 S I-PH -Correlation diffusion Vs retention

20 (twenty) cartridges from the standard production had been tested. Any of them had been tested first to an integrity test by diffusion at 690 mbar and then bacteria challenged by *Brevundimonas diminuta* $>10^7$ CFU/cm². Table 1 shows the Tests results .

As per the results the filter cartridge TEF 710 002 SI – PH - 0.2 micron is conform to the acceptance requirements.

Lot serial N#	Diffusion at 690 mbar ml/min **	Downstream Sterile	Titre Reduction
7095/10	12,0	Si	$> 1,4 \times 10^8$
7095/15	12,3	Si	$> 1,4 \times 10^8$
6827/34	13,0	Si	$> 1,2 \times 10^8$
7095/43	13,3	Si	$> 1,6 \times 10^8$
6869/05	13,4	Si	$> 1,7 \times 10^8$
6726/18	13,7	Si	$> 1,8 \times 10^8$
6726/06	14,0	Si	$> 1,8 \times 10^8$
6366/30	14,1	Si	$> 1,4 \times 10^8$
7095/03	14,3	Si	$> 1,5 \times 10^8$
6566/42	14,3	Si	$> 1,5 \times 10^8$
6827/05	14,4	Si	$> 1,3 \times 10^8$
6726/15	14,5	Si	$> 1,4 \times 10^8$
6366/14	14,6	Si	$> 1,2 \times 10^8$
6566/19	14,6	Si	$> 1,1 \times 10^8$
6366/19	14,9	Si	$> 1,4 \times 10^8$
6827/21	15,0	Si	$> 1,7 \times 10^8$
6566/02	15,0	Si	$> 1,8 \times 10^8$
6366/27	15,0	Si	$> 1,3 \times 10^9$
6827/16	15,5	No	$1,6 \times 10^6$
6869/12	16,0	No	$1,5 \times 10^6$
6366/21	17,5	Si	$> 1,7 \times 10^8$

Tab. 1. Bacteria challenge results for FilterTEF 710 002 SI - PH - 0.2 µm

** Tested in 60% IPA / 40% DI Water

Conclusions:

Based upon the results the filter cartridge TEF 7 10 002 SI - PH - 0.2 micron meets the acceptance and has to be considered a sterilizing grade filter up to a maximum diffusion value of 15.0 mL/min.

► Biological and extractables tests

► Bacteria endotoxins – current USP <85>

The test was used to measure bacterial endotoxins released from FilterTEF filter cartridge 0.2 micron rated. The test was carried out according to the Current USP<85> using the Chromogenic Method to measure the amount of endotoxins released by a filter cartridge type FilterTEF 0,2 micron.

The sample cartridge was filled with a pyrogen-free water and then treated by an ultrasonic device in order to enhance endotoxins extraction.

Water samples obtained was then submitted to the analysis.

The lab test shows bacterial endotoxins level released by the filter cartridge FilterTEF.

The test results demonstrate the absence of endotoxins release from FilterTEF cartridges.

LOT N°	METHOD	RESULT
5795/03	cUSP<85>	<0.25 EU/mL
5901/17	cUSP<85>	<0.25 EU/mL
4713/29	cUSP<85>	<0.25 EU/mL

Tabella 2. LAL test Results

► Extractables as per USP<661>

Purpose of the following test is to verify the non volatile residuals amount that can be extract by WFI. Test had been run in static condition at 70°C for 24 h.

After the extraction procedure, a sample had been dry evaporated to get the Non Volatile Residual (NVR)

LOT	NVR
5795/07	<5 mg
5901/16	<5 mg
4713/28	<5 mg

Tab. 3. FilterTEF 0.2 micron NVR by la cUSP<661>

Conclusions:

FilterTEF da 0.2 micron meet NVR by USP<661>.

►Chemical compatibility

On the following table the chemical compatibility of *FilterTEF 0.2 micron* challenged with several chemicals. However, in case of concerns, before using *FilterTEF 0.2 micron* with no experienced chemicals, please contact IPM.

CHEMICAL CLASSIFICATION	COMPOUND (Condizioni di prova: 7 giorni a 20°C)	FILTER TEF
ACIDS	Acetic acid, 90%	R
	Acetic acid, 30%	R
	Acetic acid, 10%	R
	Hydrochloric acid, conc. (35%)	R
	Hydrochloric acid, 6N (20%)	R
	Hydrochloric acid, 1N (3.3%)	R
	Nitric Acid, conc. (67%)	R
	Nitric acid, 6N (27%)	R
	Sulfuric acid, conc. (96%)	R
ALCOHOLS	Sulfuric acid, 6N (16%)	R
	Amyl alcohol	R
	Benzyl alcohol	R
	Butanol	R
	Ethanol	R
	Isopropanol	R
AROMATIC HYDROCARBONS	Methanol	R
	Benzene	R
	Toluene	R
BASES	Xylene	R
	Ammonium hydroxide, 3N (5.7%)	R
	Ammonium hydroxide, 6N (11.4%)	R
	Potassium hydroxide, 3N (15%)	R
	Sodium hydroxide, 3N (11%)	R
	Sodium hydroxide, 6N (22%)	R
ESTERS	Amyl acetate	R
	Butyl acetate	R
	Cellosolve acetate	R
	Ethyl acetate	R
	Isopropyl acetate	R
ETHERS	Methyl acetate	R
	Ethyl ether	R
	Tetrahydrofuran (THF)	R
GLYCOLS	THF in water (50:50)	R
	Ethylene glycol	R
	Glycerol	R
HALOGENATED HYDROCARBONS	Propylene glycol	R
	Carbon tetrachloride	R
	Chloroform	R
	Ethylene dichloride	R
	Methylene chloride	R
KETONES	Acetone	R
	Cyclohexanone	R
	Methyl ethyl ketone (MEK)	R
	Methyl isobutyl ketone	R
OILS	Cottonseed	R
	Peanut	R
MISCELLANEOUS	Acetonitrile	R
	Dimethylformamide (DMF)	R
	Formaldehyde (37%)	R
	Hexane	R
	Pyridine	R

Tabella 4. Chemical compatibility FilterTEF da 0.2 micron (R=Recommended, L=Limited Resistance, N=No Recommended)

► Biological safety test

► "In vitro" Biological Reactivity Test - Class VI Plastic Materials (cUSP<87>)

The purpose of this test is to evaluate the biological toxicity of the filter cartridges FilterTEF da 0,2 micron.

The sample cartridges, including the o-rings, are treated by the solutions as per procedures described in the current USP<87> in the indicated rapport weigh /volume.

Test result is indicated as a grade of reactivity where 0 is no reactivity and 4 is high reactivity.

Results in the following table:

LOT	TEST	METHOD	RESULT
5795/08	cytotoxicity	cUSP<87>	Reactivity grade 0
5901/10	cytotoxicity	cUSP<87>	Reactivity grade 0
4713/25	cytotoxicity	cUSP<87>	Reactivity grade 0

Tabella 5. tests by cUSP<87>

Conclusion:

No in vitro biological reactivity for the filter cartridges FilterTEF da 0,2 micron as per USP<87>.

► "In Vivo" Biological Reactivity Test - Class VI Plastic Materials – Safety Test
(cUSP<88>)

Purpose of the test is to evaluate the "in vivo" biological reactivity of the filter cartridges FilterTEF as per USP<88>.

Results had been evaluated as meeting the limit described in USP procedures.

LOT	TEST	RESULT
5795/10	Intracutaneous Test	Conform
	Systemic Injection Test	Conform
	Implantation Test	Conform
5901/11	Intracutaneous Test	Conform
	Systemic Injection Test	Conform
	Implantation Test	Conform
4713/22	Intracutaneous Test	Conform
	Systemic Injection Test	Conform
	Implantation Test	Conform

Tabella 6. Results by cUSP<88>

Conclusions:

No biological reactivity "in vivo" for the filter cartridges FilterTEF - 0,2 micron by USP<88>.

Physical Properties

►Hydraulic stress test

Test purpose is to demonstrate the capability of FilterTEF 0.2 micron cartridges to tolerate hydraulic stress at ambient temperature (20 ± 5 °C). 10" FilterTEF cartridges were installed inside an holder, wetted with water and fluxed at 2 bar during 20 minutes at least. After the wetting cycle was run a diffusion test.

If the cartridge passes the diffusion test, is then washed with a direct flux during 10 minutes, with 50 sudden pressure strokes from 0 to 5.0 bar. The same cartridge is then back-flushed at 2.0 bar per 10 minutes, with 50 sudden pressure strokes from 0 to 5.0 bar.

This test is repeated 50 times in both flux directions- Every 10 stress cycle every single cartridge is controlled by integrity diffusion test.

Diffusion test is performed at 690 mbarg. Acceptability limit of diffusion test was set at 15.0 mL/min. The following table reports diffusion test results run before and after the stress test.

LOT N°	DIFFUSION BEFORE STRESS TEST (mL/min)	DIFFUSION AFTER STRESS TEST (mL/min)
6827/02	12,0	13,0
6566/10	11,0	12,5
7095/26	13,5	13,0
6366/05	13,0	13,0
7095/19	11,5	12,5
6726/16	10,5	11,5
6566/12	13,0	134,5
6869/18	13,5	14,0
6566/35	13,0	14,0

Table 7-Results of hydraulic stress test run on FilterTEF filter cartridges

Test results confirm the high resistances of FilterTEF filter cartridges to hydraulic stress, even changing pressure and flux direction.

► Thermal stress test

Purpose of the test is to verify the resistance of the filter cartridge FilterTEF – at repetitive steam sterilizing cycles. Test had been run at 121°C, 35 min., per cycle.

Sample is tested by diffusion integrity test and tested each 10 cycles by diffusion.

Sterilization cycles follow the schedule below

FASE	TEMPERATURE (°C)	PRESSURE (bar)
STERILIZATION	121±1	1.14±0.04
WARMIG UP	96→121	0.00→1.15

Tab.8. Sterilizing cycle program

Diffusion integrity test run at 690 mbar with acceptance limit of di 15,0 mL/min.

Tab.9. Shows the results.

LOT	DIFFUSION BEFORE (mL/min)	DIFFUSION AFTER (mL/min)
6827/02	13,0	14,0
6566/10	14,0	14,5
7095/26	13,5	13,0
6366/05	13,0	14,0
7095/19	12,5	13,5
6726/16	14,5	13,5
6566/12	13,0	14,5
6869/18	14,5	15,0
6566/35	13,0	13,5

Tab. 9. Thermic stress FilterTEF

Conclusion:

The filter has high resistance when challenged at several sterilizing cycles.



► Differential pressure vs water flow rate

The following table shows the pressure drop Vs. air flow rate at $20\pm5^{\circ}\text{C}$ for the filter TEF per 10" module.

In the typical range of use of the filterTEF cartridges the initial Delta P are less than 0,2 bar (flow rate <1200 L/h per 10").

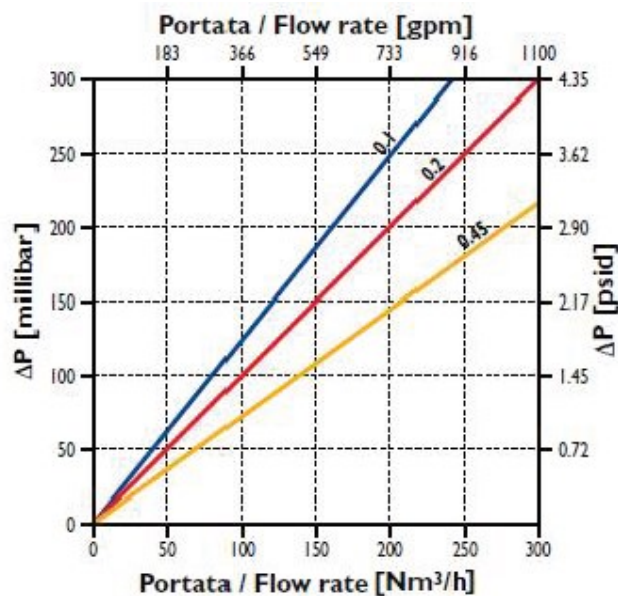


Fig. 1 – Flow rate – Delta P FilterTEF per 10" module

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