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3M Purification

3M™ Zeta Plus™ SP Series Filters

Regulatory Support File

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I. Regulatory Support Information

3M Separation and Purification Sciences Division is a leader in advanced filtration and purification solutions offering a wide range of products and services for various stages of pharmaceutical and biologics manufacturing.

3M, a U.S. based multinational high technology company with over 89,000 employees worldwide, has operations in more than 65 countries. Facilities that participate in the manufacturing of 3M™ Zeta Plus™ SP Series filters, as shown below, have quality systems that are registered to ISO 9001:2008.

Stafford Springs, CT, USA	Mazeres, France	Blacktown, Australia	Wroclaw, Poland	Columbia, MO, USA
Registered	Registered	Registered	Registered	Registered

This Regulatory Support File provides information pertinent to 3M Zeta Plus SP Series filter products in various media and product configurations. Contained herein are detailed test methods, product performance information, product specifications and regulatory compliance documentation related to pharmaceutical and biologics manufacturing processes. This regulatory support file covers media and product that are produced in multiple global locations. Where appropriate, qualitative differences in raw materials, release specifications and processes in the manufacturing location are noted throughout this document. 3M supplied documentation can be used to support risk assessments and regulatory submissions, prepare standard operating procedures and streamline testing requirements, all of which save time and cost for the manufacturer. The manufacturer of a pharmaceutical or biologic product is ultimately responsible for registration through regulatory authorities in each country or region where their product will be produced or used.

The U.S. Federal Food, Drug, and Cosmetics Act designated the United States Pharmacopeia (USP) and the National Formulary (NF) as official compendia for drugs marketed in the United States. USP-NF is a combination of two public compendia of pharmacopeia standards. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities and pharmaceutical industry to discuss various aspects of drug registration and to achieve greater international harmonization. These standards form the primary basis for technical information provided in this product support document. 3M completes a thorough annual review of the USP and ICH standards and this regulatory support file to ensure that the claims and data package are current.

The intended and prohibited uses for Zeta Plus SP series filters are stated below. Customers must evaluate and determine the suitability for your intended application.

Intended uses: Manufacturing of pharmaceutical (drug) products, including active pharmaceutical ingredients and vaccines.

Prohibited uses: As a component in a medical device that is regulated by any agency, and/or globally exemplary agencies, including but not limited to: a) FDA, b) European Medical Device Directive (MDD), c) Japan Pharmaceuticals and Medical Devices Agency (PMDA); Applications involving permanent implantation into the body; Life-sustaining medical applications; Applications requiring FDA Food Contact compliance without use restrictions.

Complementary product information, use and operating instructions and guidelines, and technical data can be found in 3M Zeta Plus SP Series filter product literature and product quality certifications. Further information can be obtained by contacting your local 3M representative.

II. Drug Master File Reference

3M™ Zeta Plus™ SP Series filters are listed in a Drug Master File (DMF) registered with the United States Food and Drug Administration (FDA).

The information contained in 3M Drug Master File may be utilized by regulatory reviewers to support a New Drug Application (NDA), Investigational New Drug Application (INDA), Abbreviated New Drug Application (ANDA), another DMF, an Export Application, or supplements to any of these.

Permission by 3M for review of a Drug Master File is granted only to appropriate United States Food and Drug Administration (FDA) or similar regulatory agency personnel as the document contains 3M proprietary information. Following the FDA Code of Federal Regulations (CFR) Title 21 Section 314.420, before FDA may review the DMF in support of an application, 3M must provide a letter of authorization permitting FDA to reference the DMF. The applicant is required to include a copy of the 3M letter of authorization in their application. 3M is required to maintain a complete list of each applicant authorized to incorporate by reference any information in the 3M DMF. 3M will update this Regulatory Support File as a routine aspect of product maintenance. Customer notification is not required in these updates. However, 3M will notify all formally registered applicants of any changes made to the DMF in the course of the required annual review. Contact 3M to initiate this process.

III. Product Family

Zeta Plus™ SP Series filter products are a family of advanced depth filters designed for optimal clarification of various bioprocess, biological and pharmaceutical fluids.

Zeta Plus SP Series filter media contains a mixture of inorganic filter aids, cellulose and a crosslinking polymer binder resin. The EXT version of SP Series has two distinct layers of filter media.

The Zeta Plus SP Series filter media offers a combination of mechanical and electrokinetic particulate removal mechanisms as a result of its physical and chemical attributes. The polymer binding resin used in these product families contains a balance of tertiary and quaternary amines resulting in an intermediate charge level relative to other 3M Zeta Plus media offerings. The surface charge enhances the filtration effectiveness by attracting negatively charged contaminants too small for removal by mechanical sieving. This intermediate charge level is recommended for fluid challenges containing a highly negatively charged product that has a potential to bind to the positively charged amine polymer. Note that the charge capacity of the media is a general attribute but not a controlled qualification or release specification. Therefore, formal process validation of charged contaminant removal must be fully assessed as part of the customer's rigorous risk management process.

A wide range of product configurations are available including media sheets, lenticular cartridges and single-use capsules.

IV. Product Descriptions

3M has global manufacturing and supply chain capabilities. The same product description as described below may be produced at multiple global locations. 3M assigns a unique ID number to each product specific to its source of supply to enable traceability.

8” Diameter Cartridges

United States Product Descriptions

Single Layer Media

Diameter Designation	Gasket Material	Grade
45109 - 8 cell	**13** – Fluorocarbon (FKM) **22** - Silicone **23** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**
45167 - 7 cell Plug-in	**03** – Fluorocarbon (FKM) **04** - Silicone **09** – Fluoropolymer (PTFE)	

Diameter Designation	Number of Cells	Configuration	Material	Gasket Material	Package	Grade
Z8FA -Plug-in	**2** - 2 cell **4** - 4 cell	**N** - None	**P** - Polypropylene	**A** - Silicone **B** – Fluorocarbon (FKM) **K** – Fluoropolymer (PTFE)	**2** - Standard	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: 451092260SP, Z8FA4NPA230SP

Dual Layer Media

Diameter Designation	Media Configuration	Number of Cells	Cartridge Construction	Gasket Material	Grade
Z08	**E** - EXT	**05** - 5 cell **06** - 6 cell **07** - 7 cell	**A** - Stainless Steel Bands **B** - Hastelloy® Bands **P** - Polypropylene Plug-in	**A** - Silicone	**05SP01A** (5 & 6 cell) **10SP01A** (5 & 6 cell) **10SP02A** (5 & 6 cell) **30SP02A** (5 & 6 cell) **30SP03A** (5 & 6 cell) **60SP01A** (5 & 6 cell) **60SP02A** (5 & 6 cell) **60SP03A** (5 & 6 cell) **60SP05A** (5 & 7 cell) **90SP05A** (5 & 7 cell) **90SP08A** (5 & 7 cell)

Product Description Example: Z08E05PA60SP05A

France and Poland Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Gasket Material	Grade
Z08	**P** - Plug-in 7 cells **P2** - Plug-in 2 cells **P4** - Plug-in 4 cells	**A** - Silicone	**05SP**

Diameter Designation	Cartridge Construction	Gasket Material	Grade
Z08	**D** - Standard 8 cells	**A** - Silicone **B** – Fluorocarbon (FKM)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: Z08P2A05SP, Z08DA60SP

Dual Layer Media

Diameter Designation	Media Configuration	Cartridge Construction	Gasket Material	Grade
Z08	**E** - EXT	**05P** - 5-cell Polypropylene Plug-in **07A** - 7-cell Stainless Steel Bands **07B** - 7-cell Hastelloy® Bands	**A** - Silicone	**05SP01A** (5 & 6 cell) **10SP01A** (5 & 6 cell) **10SP02A** (5 & 6 cell) **30SP02A** (5 & 6 cell) **30SP03A** (5 & 6 cell) **60SP01A** (5 & 6 cell) **60SP02A** (5 & 6 cell) **60SP03A** (5 & 6 cell) **60SP05A** (5 & 7 cell) **90SP05A** (5 & 7 cell) **90SP08A** (5 & 7 cell)

Product Description Example: Z08E07AA60SP02A

Australia Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Gasket Material	Grade
Z08	**C** - 8" 9-cell DOE **B** - 8" 7-cell Plug-in	**13** – Fluorocarbon (FKM) **22** - Silicone **23** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: Z08C2260SP

12” Diameter Cartridges

United States Product Descriptions

Single Layer Media

Diameter Designation	Material	Gasket Material	Grade
45244 - 9 cell DOE **45237** - 12 cell DOE **45245** - 16 cell DOE	**01** - Polypropylene (PP) **02** - Mineral-filled PP **03** - PP, Hastelloy® Bands	**A** - Silicone **B** – Fluorocarbon (FKM) **E** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: 4523702A90SP

France and Poland Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Opt Lifting Handle	Gasket Material	Grade	Opt Material
Z12	**C** - 9 cells /small **B** - 12 cells **D** - 16 cells[1] **M** –15 cells, netting **S** - 7 cells	**H**[2] – with Handle	**A** - Silicone **B** – Fluorocarbon (FKM)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**	**H**[3] – Hastelloy® Bands

1. 15 cells for 05SP media
2. Omit “H” from product description if lifting handle is not required.
3. “H” for Hastelloy® bands. Omit “H” for Stainless Steel Bands.

Product Description Example: Z12DA90SP

Australia Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Gasket Material	Grade
Z12	**C** - 9-cell **D** - 16-cell	**A** - Silicone **B** – Fluorocarbon (FKM) **E** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: Z12DA90SP

16” Diameter Cartridges

United States Product Descriptions

Single Layer Media

Diameter Designation	Configuration	Gasket	Grade	Opt. Lifting Handle
Z16	**P** - 14 cell **H** - High area[2] **R** - 14 cell with Hastelloy® bands **T** - High area with Hastelloy® bands	**A** - Silicone **B** – Fluorocarbon (FKM) **E** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**	**H** - with Handles[1]

1. Omit “H” from product description if lifting handle is not required.
2. High Area Cell Count – 30SP & 50SP 16 cell; 60SP & 90SP 17 cell; Not available for 05SP & 10SP. Bodyfeed cartridge available, please order 45802 (16”, 9 cell)

Product Description Example: Z16PA60SP

Dual Layer Media

Diameter Designation	Media Configuration	Number of Cells	Cartridge Construction	Gasket Material	Grade
Z16	**E** - EXT	**01** - 1 cell **02** - 2 cell **08** - 8 cell **12** - 12 cell	**A** - Stainless Steel Bands	**A** - Silicone	**05SP01A** **10SP01A** **10SP02A** **30SP02A** **30SP03A** **60SP01A** **60SP02A** **60SP03A** **60SP05A** **90SP05A** **90SP08A**

Product Description Example: Z16E08AA60SP05A

Australia Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Gasket Material	Grade	Opt Lifting Handle
Z16	**M** - 14-cell	**A** - Silicone **B** – Fluorocarbon (FKM) **E** - Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **30SP** **60SP** **90SP**	**H**[1] - with Handles

1. Omit “H” from product description if lifting handle is not required.

Product Description Example: Z16MA60SP

France and Poland Product Descriptions

Single Layer Media

Diameter Designation	Cartridge Construction	Opt Lifting Handle	Gasket Material	Grade	Opt Material
Z16	**M** - 14 cells, netting **P** - 14 cells, netting **D** - 15 cells **S** - 9 cells **H** – High Area[1], netting, Stainless Steel Bands **T** – High Area[1], netting, Hastelloy Bands **R** - 14 cells, netting, Hastelloy Bands	**H** – with Handle	**A** - Silicone **B** - Fluorocarbon (FKM) **E** – Fluoropolymer (PTFE)	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**	**H**[2]

1. 17 cells for 60SP, 90SP; 16 cells for 30SP and 50SP
2. "H" for Hastelloy bands for M, D, S only. Omit "H" for Stainless Steel Bands

Product Description Example: Z16MA90SP

Dual Layer Media

Diameter Designation	Media Configuration	Number of Cells	Cartridge Construction	Gasket Material	Grade
Z16	**E** - EXT	**01** - 1 cell **02** - 2 cell **08** - 8 cell **12** - 12 cell	**A** - Stainless Steel Bands **B** - Hastelloy® Bands	**A** - Silicone	**05SP01A** **10SP01A** **10SP02A** **30SP02A** **30SP03A** **60SP01A** **60SP02A** **60SP03A** **60SP05A** **90SP05A** **90SP08A**

Product Description Example: Z16E08AA90SP05A

Zeta Plus™ Laboratory Capsules

United States, Poland and France Product Descriptions

Single Layer Media

Diameter Designation	Configuration	Grade
BC0025 **BC0025**	**L** - Luer **S** - Sanitary	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: BC0025L60SP

Dual Layer Media

Diameter Designation	Configuration	Grade
BC0025 **BC0025**	**L** - Luer **S** - Sanitary	**05SP01A** **10SP01A** **10SP02A** **30SP02A** **30SP03A** **60SP01A** **60SP02A** **60SP03A** **60SP05A** **90SP05A** **90SP08A**

Product Description Example: BC0025S60SP05A

Zeta Plus™ Scale-Up Capsules

United States and Poland Product Descriptions

Single Layer Media

Diameter Designation	EFA (cm^2)	Capsule Material	Grade
E	**0170** **0340** **1020**	**FSA** - Polysulfone	**05SP** **10SP** **30SP** **50SP** **60SP** **90SP**

Product Description Example: E0340FSA60SP

Dual Layer Media

Diameter Designation	EFA (cm^2)	Capsule Material	Grade
E	**0170** **0340** **1020**	**FSA** - Polysulfone	**05SP01A** **10SP01A** **10SP02A** **30SP02A** **30SP03A** **60SP01A** **60SP02A** **60SP03A** **60SP05A** **90SP05A** **90SP08A**

Product Description Example: E0170FSA60SP05A

Zeta Plus™ Production Capsules

United States and Poland Product Descriptions

Single Layer Media

Diameter Designation	Configuration	Number of Cells	Gasket Material	Grade
E16	**E** - Standard **R** - Alkaline resistant	**01** - 1 cell **11** - 11 cell	**A** - Silicone	**05SP**[1] **10SP** **30SP** **50SP** **60SP** **90SP**

1. 05SP is available in 7 cell 1.6 m^2 capsule format, the product description for a standard 1.6 m^2 capsule with 05SP is E1607A05SP

Product Description Example: E16E01A90SP

Dual Layer Media

Diameter Designation	Configuration	Number of Cells	Gasket Material	Grade
E16	**E** - Standard **R** - Alkaline resistant	**01** - 1 cell **07** - 7 cell	**A** - Silicone	**05SP01A** **10SP01A** **10SP02A** **30SP02A** **30SP03A** **60SP01A** **60SP02A** **60SP03A** **60SP05A** **90SP05A** **90SP08A**

Product Description Example: E16E07A05SP01A

Zeta Plus™ Production Capsule System Manifold

United States and Poland Product Descriptions

Product Description
6128901 - Standard Set **6129001** - Alkaline Resistant Set

Product Description Example: 6128901

V. Product Design and Materials of Construction

All components used in the manufacture of 3M™ Zeta Plus™ SP Series filter products are traceable. Intermediate products are packaged and labeled throughout the manufacturing process to provide complete traceability from the raw materials to media batch to finished product.

All grades of the Zeta Plus SP Series filter media are composed of the same materials of construction at various ratios. Therefore, many of the test results reported herein are generally applicable to all grades and product configurations.

Multiple manufacturing facilities in various global locations produce Zeta Plus SP Series filter products. Some of the raw materials are secured locally to enable high service levels, supply chain redundancy and security, and to maintain a cost efficient manufacturing infrastructure. Raw materials are purchased consistent with global specifications.

A. Media

Zeta Plus SP Series filter media contains a mixture of inorganic filter aid, cellulose and a crosslinking polymer binder resin. The media is produced by a wetlaid process.

Media or filter sheets may be die cut to various shapes and dimensions per specific customer specifications. Filter sheets are generally used in commercially available filter presses. Each distinct pattern is assigned a unique stock number.

Zeta Plus EXT version of SP Series filter media consist of two distinct layers, or “zones”, of filter media with the upstream zone more open than the downstream zone. The media used for each layer is a standard grade. This structure enhances the contaminant holding capacity of the filter media, since larger particles are trapped in the upstream zone of the more open filter media and smaller particles are trapped in the downstream zone, reducing premature plugging and helping extend service life.

B. Cartridges

The lenticular cells of cartridges are comprised of single or dual opposing layers of the filter media and an inner cell separator with a polymeric molded edge seal. The lenticular cells are sealed to one another by ring seals that are aligned to the inner fluid effluent core and rest on the media under predetermined compression by three 316 stainless steel or Hastelloy® binder bands. Netting is added to selected model numbers. Each cartridge has two gaskets one at the top and one at the bottom. Depending on the cartridge configuration, the three standard gasket materials that may be offered are silicone, fluorocarbon (FKM) and fluoropolymer (PTFE).

Filter cartridges are available in 8", 12" and 16" nominal diameters, with surface areas ranging from 0.26 m² to 3.9 m² per cartridge. The cartridge lenticles have an outside-to-in flow path. The flow passes through the filter media and is directed to a central exit flow path along the separators.

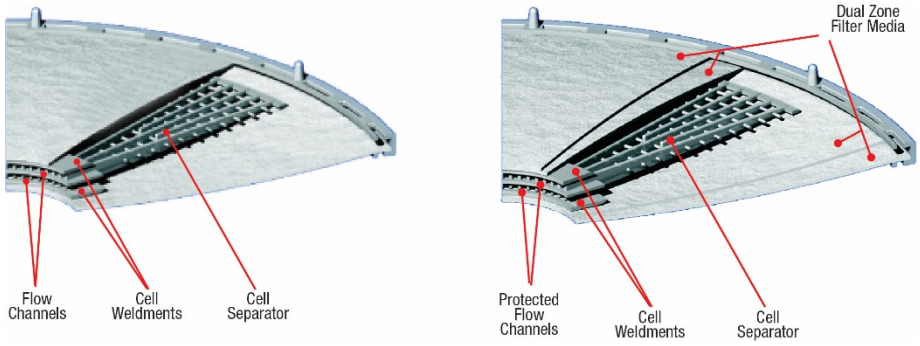


Figure 1a. Zeta Plus™ cartridge lenticle configuration with single media layer or dual media layers

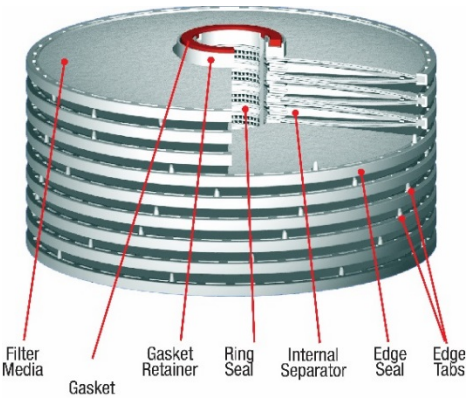


Figure 1b. Zeta Plus™ cartridge and components

Figure 1c. Zeta Plus™ cartridges shown with housings

C. Capsules

There are three capsule configurations for the Zeta Plus™ filters: Laboratory, Scale-up and Production capsules.

Laboratory capsule (BC0025) is constructed by compressing the single or dual layer filter media between the inlet and outlet capsule components, then overmolding this entire unit with a glass fiber filled polypropylene. The Laboratory capsule is available with either luer lock or 1/2" mini sanitary matched inlet and outlet connections. The laboratory capsule has a surface area of 25 cm².

Scale-up capsules are constructed from a lenticular media cell design having a diameter of 8". The lenticle comprises single or dual opposing layers of the filter media and an inner separator with a polymeric molded edge seal. This lenticle is first compressed and then held together by injection molding at the outer and inner diameter by a thermoplastic resin, which simultaneously seals all edges and forms the inner fluid outlet manifold. A polypropylene spacer is placed between the lenticles in 3-cell design capsule. The lenticles have an outside-to-in flow path. The flow passes through the filter media and is directed to a central exit flow path along the separators. Scale-Up capsules have three configurations with surface areas of 170 cm², 340 cm² and 1020 cm² per capsule. For the 170 cm² lenticle, one of the opposing filter media layers is replaced with an injection molded polypropylene disk, thereby, reducing the accessible surface area by a factor of two. The 1020 cm² capsules contain three stacked and sealed lenticles. The lenticles, or lenticle stack, are sealed to the outlet side of the capsule with a polypropylene support ring and fluorocarbon o-ring. The top and bottom pieces of the capsule are sealed together by a thermal bond. The Scale-up capsules have mini sanitary connections on the inlet and outlet.

Production capsules are also constructed from a lenticular media cell design having a diameter of 16". Each lenticle has two opposing layers of the filter media and an inner separator with a polymeric molded edge seal. The lenticle is first compressed and then held together by injecting molding at the outer and inner diameter by a thermoplastic resin, which simultaneously seals all edges and forms the inner fluid outlet manifold. A polypropylene spacer is placed between the lenticles in 7-cell and 11-cell capsules. The lenticles have an outside-to-in flow path. The flow passes through the filter media and is directed to a central exit flow path along the separator. The production capsules have three single-use capsule configurations. The 0.23 m² capsule is designed for single or dual layer media and has one lenticle. The 1.6 m² capsule has seven (7) lenticles of dual layer media. The 2.5 m² capsule has eleven (11) lenticles of single layer media.

The outermost lenticles of the lenticle stack have a male and female connectors thermally attached to the lenticle stack. The connectors use silicone o-rings to seal adjacent capsules or manifolds. The top and bottom capsule shells are sealed together by a thermal bond. The multicell production capsule has a self-guiding locking mechanism for a robust capsule-to-capsule connection. The standard production capsule material is translucent polycarbonate. An opaque polyphenylene/oxide polystyrene, alkaline resistant capsule material option is available, enabling exposure to strong bases. The multicell production capsules have two handles for convenient loading and unloading.

A set of manifolds is required for connecting the capsules to external components of the purification train. The production capsule manifolds have 1.5" sanitary connections on the inlet and outlet.

The Zeta Plus™ Production capsules may be used in a multi-stage filtration or purification train with a single 3M™ Encapsulated System holder. The Production capsules of the same media configuration or of the different media configurations can be installed in a single 3M™ Encapsulated System holder. Additionally, one of the stages may include 3M™ Emphaze™ products. An extra pair of manifolds is required between each stage of the multi-stage train within the 3M Encapsulated System holder.

1) Zeta Plus™ Laboratory Capsules

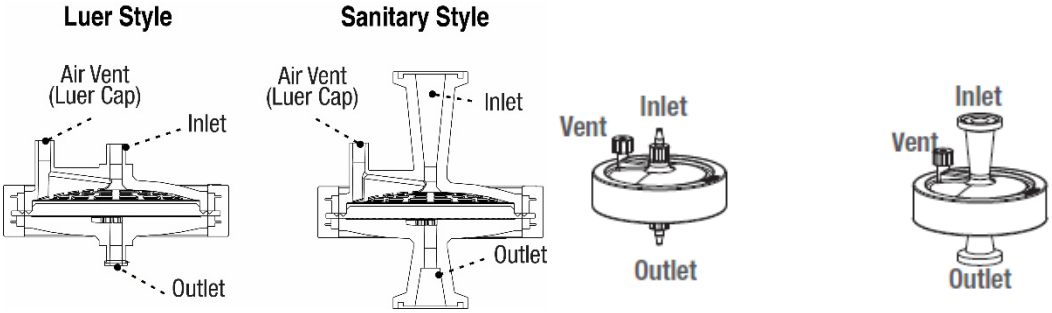


Figure 2. Zeta Plus™ Laboratory capsules

2) Zeta Plus™ Scale-Up Capsules

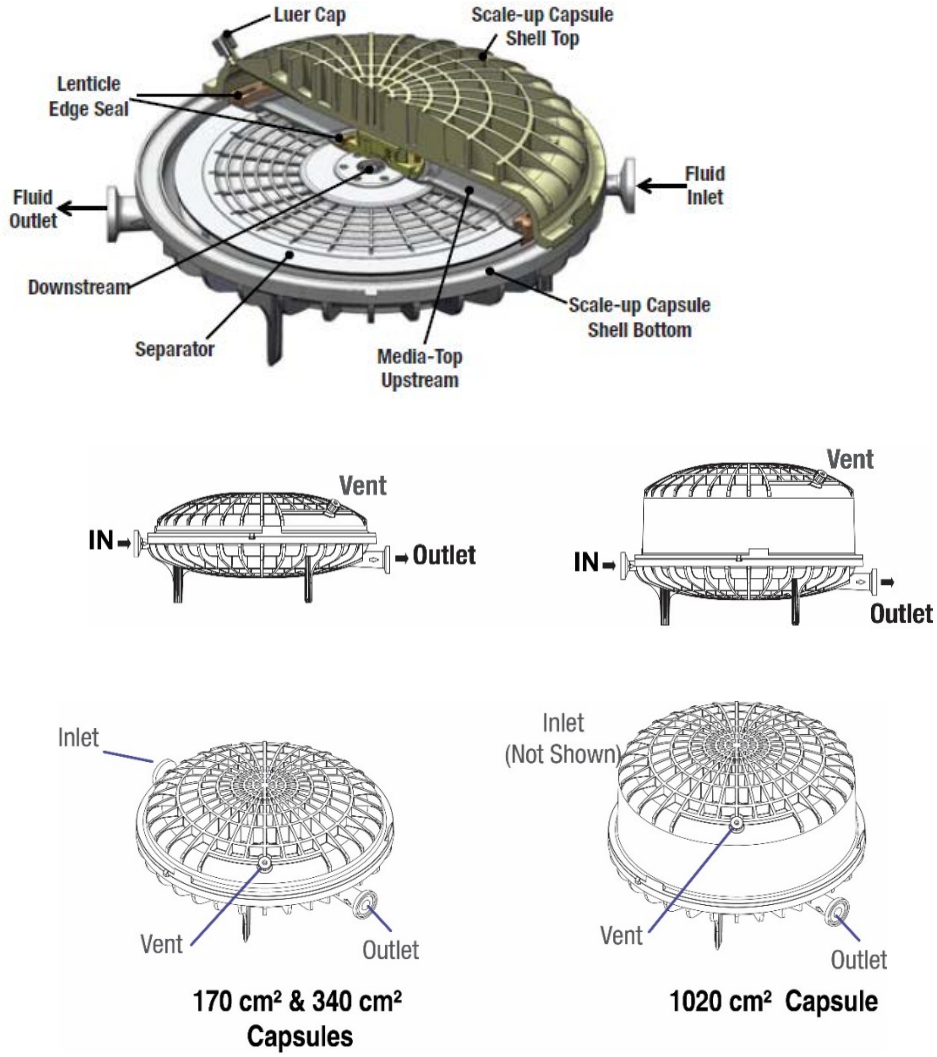
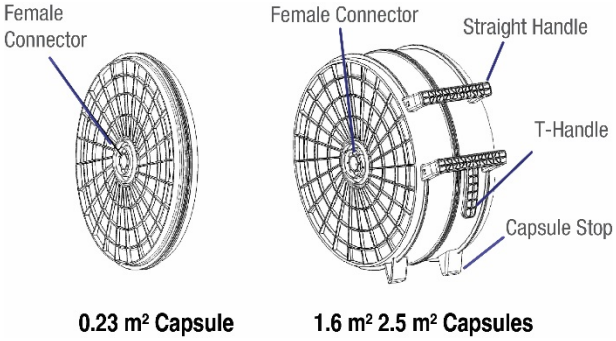


Figure 3. Zeta Plus Scale-up capsules

3) Zeta Plus™ Production Capsules



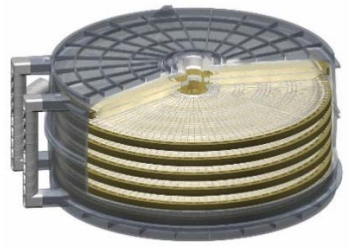


Figure 4a. Zeta Plus™ Production capsules

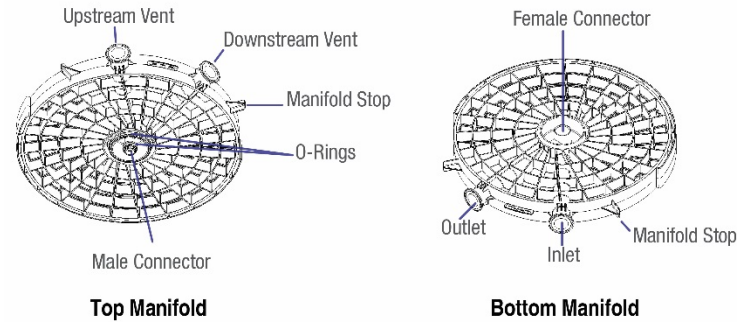


Figure 4b. Zeta Plus™ Production capsule manifolds

Figure 4c. Zeta Plus™ Production capsules installed in holders

D. Materials of Construction

The materials of construction for each filter configuration are summarized in Tables 1a through 1d.

Table 1a. Materials of Construction - Filter Cartridges

Part Type	Materials
Filter Media	Natural Silica, Cellulose, Polymer Resin
Separators	Polypropylene or Mineral-filled Polypropylene
Netting*	Polypropylene
Edge Seal	Polypropylene or Mineral-filled Polypropylene (single layer media) or Thermoplastic Elastomer (dual layer media)
Ring Seal	Polypropylene
Gasket Retainers	Polypropylene or Mineral-filled Polypropylene
Gaskets	Silicone or Fluorocarbon (FKM) or Fluoropolymer
Binder Bands	316 Stainless Steel or Hastelloy®
8" cartridge Plug-in Unitizing Post	Polypropylene

* Specific 12" and 16" cartridges

Table 1b. Materials of Construction - Laboratory Capsules

Part Type	Materials
	BC0025 (25 cm^2)
Filter Media	Natural Silica, Cellulose, Polymer Resin
Shells	Polypropylene
Ring Seal (dual layer media)	Polypropylene
Edge Seal Overmold	Glass Fiber Filled Polypropylene
Luer cap & luer-barb connector	Polypropylene

Table 1c. Materials of Construction - Scale-Up Capsules

Part Type	Materials		
	E0170 Capsule (170 cm^2)	**E0340 Capsule (340 cm^2)**	**E1020 Capsule (1020 cm^2)**
Filter Media	Natural Silica, Cellulose, Polymer Resin		
Separators	Polypropylene		
Spacers	N/A		Polypropylene
Flow Inhibitor Disc for E0170	Polypropylene	N/A	
Edge Seal	Thermoplastic Elastomer		
Inner Seal Overmold	Thermoplastic Elastomer		
Endcap	Thermoplastic Elastomer		
Shells	Polysulfone		
Back-up O-ring	Polypropylene		
O-ring	Fluorocarbon		
Luer Cap	Polypropylene		

Table 1d. Materials of Construction - Production Capsules

Part Type	Materials	
	E16E01, E16R01 Capsules (0.23 m^2)	**E16E07, E16R07, E16E11, E16R11 Capsules (1.6 and 2.5 m^2)**
Filter Media	Natural Silica, Cellulose, Polymer Resin	
Separators, Spacers	Polypropylene	
Edge Seal	Thermoplastic Elastomer	
Ring Seal	Thermoplastic Elastomer	
Connectors (Male & Female)	Polypropylene	
Shells	Either Polycarbonate or Polyphenylene Oxide/Polystyrene	
O-ring Retainer	Either Polycarbonate or Polyphenylene Oxide/Polystyrene	
O-rings	Silicone	
Handles	N/A	Nylon
Manifold	Polycarbonate or Polyphenylene Oxide/Polystyrene	

The wetted surface areas of components in Zeta Plus™ filter cartridges and capsules are listed in Tables 2a through 2d. For o-rings, it is assumed that 50% of surface area is wetted.

The wetted area calculations are based on 3D models where all geometries are represented by a finely spaced discrete set of points and curves are approximated by linear interpolation between these discrete points. A built-in numerical quadrature algorithm is used to estimate the surface area and volume of this geometry. With tolerances allowed in filter components dimension, the listed wetted surface areas represent the nominal values.

Table 2a. Wetted Surface Areas of Cartridge Components

Cartridge Components	Wetted Surface Area[1] [cm^2]		
	8" Cartridge	12" Cartridge	16" Cartridge
Separator (per lenticle)	415	1373	4361
Netting[2] (per lenticel)	-	5970	12900
Edge seal (per lenticle)	174	312	426
Ring seal (per lenticle)	23	12	22
Gasket Retainer (each)	46	57	57
Gasket (each)	28	37	37
Binder Bands	19	28	28
45167, Z8FA, Z08E05, 8" Plug-in Unitizing Post	397	--	--

[1] Media surface areas are listed in Table 6 of Section VI F
[2] Specific 12" and 16" cartridges

Table 2b. Materials of Construction - Laboratory Capsules

Part Type	Wetted Surface Area [cm^2]
Shell (Inlet – Luer)	41
Shell (Inlet – Sanitary)	48
Shell (Outlet - Luer)	54
Shell (Outlet – Sanitary)	58
Ring Seal (dual layer media)	36
Edge Seal	Non-wetted Surface

Table 2c. Wetted Surface Areas of Scale-Up Capsule Components

Scale-up Capsule Components	Wetted Surface Area [cm^2]
Separator (per lenticle)	324
Spacer for E1020	3.7
Flow Inhibitor Disc for E0170	439
Edge Seal for E0170 (per lenticle)	250
Edge Seal for E0340 & E1020 (per lenticle)	208
Inner Seal (per lenticle)	47
EndCap	14.7
Shell Top E0170 & E0340	388
Shell Top E1020	679
Shell Bottom	420
Back-up O-ring	2.5
O-ring	1.4

Table 2d. Wetted Surface Areas of Production Capsule Components

Production Capsule Components	Wetted Surface Area [cm^2]
Separator assembly	2,178
Spacer	825
Edge Seal, 1-cell or 11-cell (per lenticle)	592
Inner Seal, 1-cell or 11-cell (per lenticle)	68
Edge Seal, 7-cell (per lenticle)	516
Inner Seal, 7-cell (per lenticle)	79
Connectors (Male and Female)	377
Capsule shells (2), 1-cell	3,554
Capsule shells (2), multi-cell	5,477
O-ring large retainer	28
O-ring large	14
O-ring small	4
Manifold (Total Top and Bottom)	1,047

VI. Product Specifications and Operation Parameters

A. Product Release Specifications

The product specifications verified during filter manufacturing and prior to the release of media lots are:

1) Specific Dry Sheet Weight
2) Pressure Drop at constant air flow
3) Wet Tensile Strength
4) Calcium Extraction
5) Iron Extraction
6) Color Extraction
7) Organic Extraction
8) Endotoxin Extraction - *Limulus* Amebocyte Lysate (LAL) bacterial endotoxin Reactivity

The specification limits for each Zeta Plus SP media grade are presented in Table 3. The EXT media grades have the same specifications of the tighter media layer. The specifications are also included in Certificate of Quality (COQ), which is provided with each product shipment.

Table 3. Product Release Properties of Zeta Plus™ SP Series Filters

Product Release Properties	Specifications (US: USA; FR: France; PL: Poland)							
	01SP	05SP	10SP	30SP	50SP	60SP	90SP	Units
Pressure Drop at Air Flow	≤ 2.8	2.7 – 5 (US 2.0 – 5)	8.5 – 13 (FR 6.3 – 13.2)	16 – 26 (FR 13.5 – 33)	50 – 68 (FR 45 – 68)	81 – 107 (FR 68 – 112.5)	148 – 202 (FR 112.5 – 215)	Inch H_2O
Wet Tensile Strength	≥ 1.5	≥ 3.0	≥ 3.0	≥ 4.0 (FR ≥ 3.5)	≥ 5.0 (FR ≥ 4.0)	≥ 5.5 (FR ≥ 4.5)	≥ 6.5 (FR ≥ 5.0)	Kg/in
Ca Extraction	≤ 0.040 (FR, PL ≤ 0.080)	≤ 0.040	≤ 0.040	≤ 0.040	≤ 0.040	≤ 0.040	≤ 0.040	mg/g
Fe Extraction	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	mg/g
Color Extraction	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	Color Units
Organic Extraction	NA	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	Wt. %
Endotoxin Extraction	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	EU/mL

Product Release Properties	Specifications (US: USA; FR: France; PL: Poland)						
	05SP01	10SP01	10SP02	30SP02, 30SP03	60SP02, 60SP03, 60SP05	90SP05, 90SP08	Units
Pressure Drop at Air Flow	2.7 - 5 (US 2.0 – 5)	8.5 – 13 (FR 6.3 – 13.2)	8.5 – 13 (FR 6.3 – 13.2)	16 – 26 (FR 13.5 – 33)	81 – 107 (FR 68 – 112.5)	148 – 202 (FR 112.5 – 215)	Inch H_2O
Wet Tensile Strength	≥ 3.0	≥ 3.0	≥ 3.0	≥ 4.0 (FR ≥ 3.5)	≥ 5.5 (FR ≥ 4.5)	≥ 6.5 (FR ≥ 5.0)	Kg/in
Ca Extraction	≤ 0.040 (FR, PL ≤ 0.080)	≤ 0.040 (FR, PL ≤ 0.080)	≤ 0.040	≤ 0.040	≤ 0.040	≤ 0.040	mg/g
Fe Extraction	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	≤ 0.010	mg/g
Color Extraction	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	≤ 8.0	Color Units
Organic Extraction	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	≤ 0.25	Wt. %
Endotoxin Extraction	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	< 0.25	EU/mL

B. Installation and Operation Instructions

The installation and operation of Zeta Plus™ SP Series filter products should follow appropriate instructions for each filter configuration. Always operate within the pressure and temperature design limits of the housing and the filter product.

Note: Installation and Operation Instructions are available upon request from your local representative

Prior to filtration operation, the end-user should verify that the housing for filter cartridges is integral and filter cartridges have been properly installed and sealed in a filter housing, and that Zeta Plus™ Production Capsules have been properly installed in the system holder. Therefore, qualification test should be performed per recommended test procedure contained in 3M's Installation and Operating Procedures manual.

C. Minimum Required Preconditioning Flush

Zeta Plus™ depth filters are comprised primarily of natural products and are classified per FDA CFR Title 21.211.72 as fiber-releasing filters. Trace amounts of polymer resin, cellulosic fibers and natural extractables such as endotoxin, beta-glucan, and inorganic ions, are released by these filters during use, especially initial use. Therefore, 3M requires that customers flush the filters before exposure to their product. Zeta Plus depth filters can be flushed with hot or cold water or buffer at temperature and pressure not to exceed the maximum values of corresponding product configuration. If the filter is autoclaved or *in-situ* steam sterilized, 3M requires that it be flushed after sterilization per preconditioning flush protocols including diverting the initial surge of filter extractables away from the processes.

Detailed preconditioning flush protocols are provided in the 3M Installation and Operating Instructions for these products. The required minimum preconditioning flush volume for each filter configuration is provided in Table 4. The recommended flux of required preconditioning flush is 1200 L/m^2/hour (LMH) for cartridges and 210 LMH for capsules. Pressure drop across the filter should not exceed 2.4 bar [35 psid]. The data package of effluent quality presented in this Regulatory Support File is developed based on the recommended flux of the required preconditioning flush for cartridges.

Table 4. Minimum Required Preconditioning Flush Volume and Recommended Flux

Minimum Required Preconditioning Flush Volume	All Products	54 L/m^2
Recommended Flux of Required Preconditioning Flush	Cartridges	1200 LMH
	Capsules	210 LMH

D. Clean-in-Place

Zeta Plus™ SP Series filter products can be treated with 1M NaOH or 5% NaClO post-use. Note that the polycarbonate (standard) Production Capsules can NOT be exposed to these solutions.

Reference:
Laboratory Report: Lab-10166

E. Autoclave or *in-situ* Steam Sterilization

Zeta Plus™ SP Series filter products can be autoclaved or *in-situ* steam sterilized per recommended conditions listed in Table 5. Studies were conducted to ensure sterility after autoclave or *in-situ* steam sterilization.

If the filter is autoclaved or *in-situ* steam sterilized, 3M requires that it be flushed after sterilization.

Table 5. Product Autoclave or SIP Conditions

Autoclave / Steam-in-Place Parameters	Cartridges	*in situ* steam sterilization, 30 minutes @126 ºC (259 ºF) (3 cycles)
	Laboratory Capsules	Autoclave only, 30 minutes @121 ºC (250 ºF) (1 cycle)
	Scale-Up Capsules	Autoclave only, Gravity cycle 120 minutes @121 ºC (250 ºF) (1 cycle), or Pre-vac cycle 40 minutes @121 ºC (250 ºF) (1 cycle)
	Production Capsules	Autoclave only, Pre-vac cycle 40 minutes @121 ºC (250 ºF) (1 cycle)

Additionally, the Total Organic Carbon, pH and Conductivity of media extract were measured after autoclave and compared to those of media prior to autoclave. The comparison data are presented in sub-Sections A, B and C under Section VIII Effluent Quality.

References:
3M SOP: 10L.600.129 (ORIG)
Laboratory Report: SASS - 2460

F. Effective Filtration Surface Area & Minimum Required Preconditioning Flush Volume

The minimum required preconditioning flush volume is 54 L/m^2. For each filter configuration it is calculated based on its effective filtration area and is presented in Table 6.

Table 6. Effective Filtration Surface Area & Minimum Required Preconditioning Flush Volume

Cartridge Configurations	Nominal Effective Surface Area	Preconditioning Flush Vol [L]
Laboratory Capsule Filter	25 cm^2	0.14
45109 (8" diameter cartridge, 8-cell)	0.26 m^2	14
45167 (8" diameter cartridge, 7-cell O-ring plug-in)	0.23 m^2	12
Z8FA2NPx2 (8" diameter, 2-cell plug-in)	0.065 m^2	3.5
Z8FA4NPx2 (8" diameter, 4-cell plug-in)	0.13 m^2	7.0
Z08E05 (8” diameter cartridge, 5-cell plug-in)	0.16 m^2	8.6
Z08E06 (8” diameter cartridge, 6-cell)	0.20 m^2	11
Z08E07 (8” diameter cartridge, 7-cell)	0.23 m^2	12
45244 (12" diameter cartridge, 9-cell)	0.85 m^2	46
45237 (12" diameter cartridge, 12-cell)	1.1 m^2	59
45245 (12" diameter cartridge, 16-cell)	1.5 m^2	81
Z12E11 (12” diameter cartridge, 11-cell)	1.0 m^2	54
Z16P (16" diameter cartridge, 14-cell)	3.2 m^2	173
Z16H (16" diameter cartridge, 16-cell) 30SP & 50SP only	3.7 m^2	200
Z16H (16" diameter cartridge, 17-cell) 60SP & 90SP only	3.9 m^2	211
Z16E01 (16” diameter cartridge, 1-cell)	0.23 m^2	12
Z16E02 (16” diameter cartridge, 2-cell)	0.46 m^2	25
Z16E08 (16” diameter cartridge, 8-cell)	1.8 m^2	97
Z16E12 (16” diameter cartridge, 12-cell)	2.7 m^2	146
E0170 (Zeta Plus™ Scale-Up Capsule)	0.017 m^2	0.9
E0340 (Zeta Plus™ Scale-Up Capsule)	0.034 m^2	1.8
E1020 (Zeta Plus™ Scale-Up Capsule)	0.102 m^2	5.5
E16E01 & E16R01 (capsule)	0.23 m^2	12
E16E07 & E16R07 (capsule)	1.6 m^2	86
E16E11 & E16R11 (capsule)	2.5 m^2	135

G. Operating Parameters

Table 7. Product Operating Conditions		
Maximum Operating Pressure	Laboratory Capsule Filters	2.8 bar (40 psig) maximum inlet pressure
	Scale-Up Capsule Filters	3.1 bar (45 psig)
	Production Capsule Filters	3.4 bar @40 ºC (50 psig @104 ºF)
Maximum Differential Pressure Forward	All Products	2.4 bar (35 psig)
Maximum Operating Temperature	Cartridge Filters	82 ºC (180 ºF)
	Laboratory Capsule Filters	40 ºC (104 ºF)
	Scale-Up Capsule Filters	
	Production Capsule Filters	
Minimum Required Preconditioning Flush Volume	All Products	See Section VI. C.
Recommended Flux of Required Preconditioning Flush	Cartridges	
	Capsules	
Autoclave / Steam-in-Place Parameters	Cartridges	See Section VI. E. Autoclave or Steam Sterilization
	Laboratory Capsules	
	Scale-Up Capsules	
	Production Capsules	

VII. Performance Verification

Zeta Plus media has variations within each manufacturing lot and from lot-to-lot. The following data package is based on test data of a limited number of manufacturing lots from each global facility and should be considered typical values. On-going annual review and revalidation tests will expand the statistics to characterize the anticipated variations.

A. Media Pressure Drop vs. Water Flow Rate

The 90-mm discs of Zeta Plus media 30SP, 50SP, 60SP and 90SP were tested for pressure drop as a function of water flow rate with 18 Megohm water (25°C), as shown in Figure 5a.

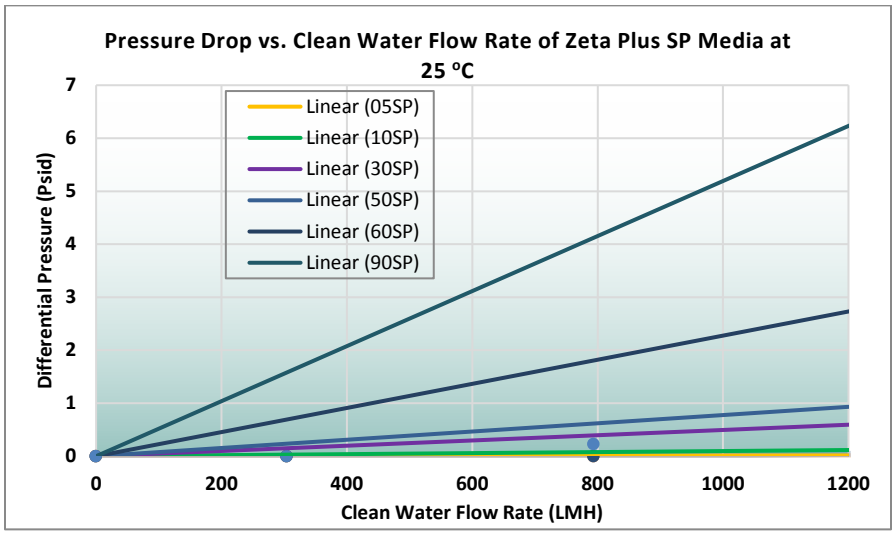


Figure 5a. Pressure drop versus water flow rate of Zeta Plus SP media

The 90-mm discs of Zeta Plus media 60SP manufactured at different global manufacturing facilities were tested for pressure drop as a function of water flow rate with 18 Megohm water (25°C), as shown in Figure 5b.

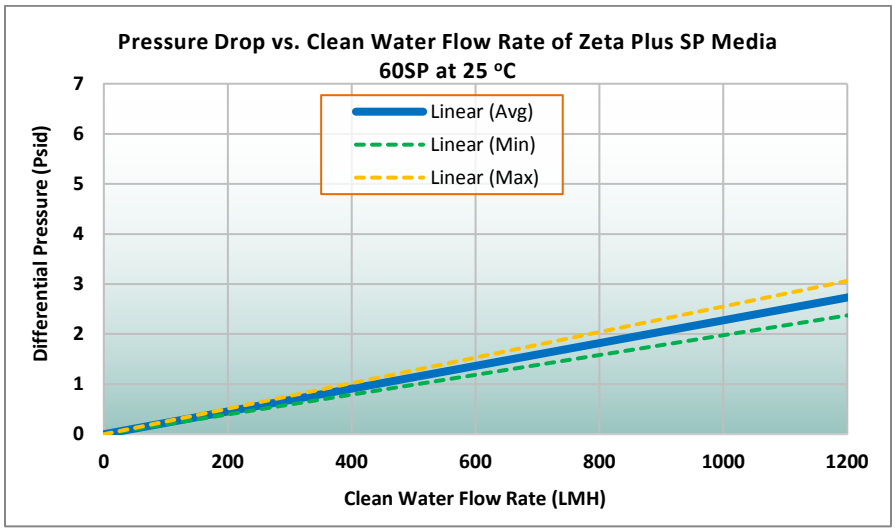


Figure 5b. Pressure drop versus water flow rate of Zeta Plus media 60SP

The 90-mm discs of Zeta Plus media 60SP05A made at different global manufacturing facilities were tested for pressure drops as a function of water rate with 18 Megohm water (25°C), as shown in Figure 5c.

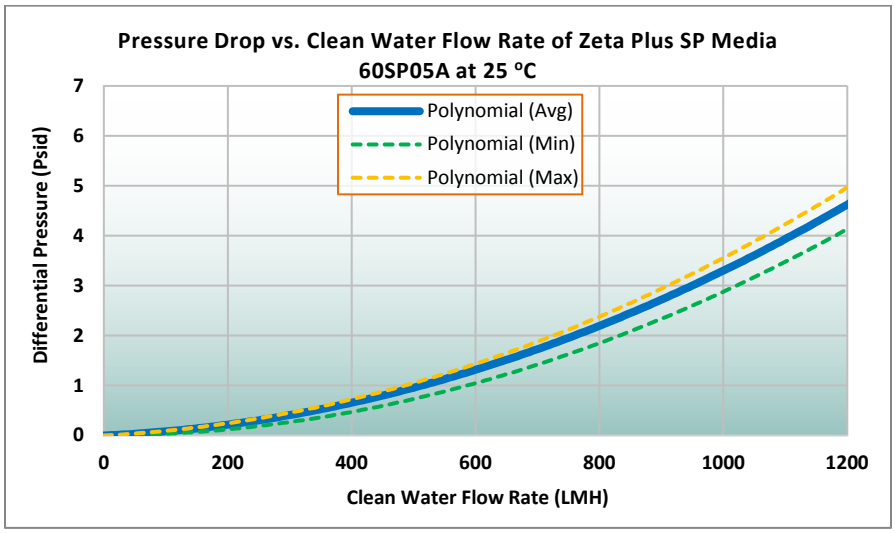


Figure 5c. Pressure drop versus water flow rate of Zeta Plus media 60SP05A

References:
3M SOP: 10L.300.004(C)
Laboratory Report: Lab-12893, Lab-13005

VIII. Effluent Quality

Various regulatory organizations require that equipment used in pharmaceutical manufacturing that is in direct contact with the drug product should not add to or change the drug in any way other than what is intended by the manufacturer. However, as of December 2016, USP does not provide specific guidance (test methods or specifications) on how to conduct extractable/leachable product testing for single use systems.

Distribution of Responsibility

3M Separation and Purification Sciences Division has adopted the following supplier collaborative model (D. Jenke, Pharma Ed Conference on Extractables & Leachables, keynote address Oct 2011) relative to Extractable and Leachable evaluation.

Shared Responsibility of Supplier and Producer

1. It is the responsibility of suppliers of plastic materials or systems to provide users with a full and complete composition of their material or system.

2. It is the responsibility of the producer to supply regulators with a full and complete leachables assessment for their finished therapeutic product.

3. It is the shared responsibility of the producer and supplier to collaborate on obtaining extractables information and in so doing increases the effectiveness and efficiency of extractables studies.

In this Regulatory Support File, 3M provides effluent quality data relating to preconditioning flush.

Table 8. Reference Industry Standards

USP Standards	Applicable Methods
<643>	Total Organic Carbon
<645>	Conductivity
<791>	pH
<232>, <233>, ICH* Q3D	Elemental Impurities
<788>	Particulate Matter
<85>	Bacterial Endotoxin
<661>	Containers - Plastics

* ICH – International Conference of Harmonization, Guideline For Elemental Impurities, Q3D, Dec. 16, 2014

Zeta Plus media has variations within each manufacturing lot and from lot-to-lot. The following data package is based on test data of a limited number of manufacturing lots from each global facility and should be considered typical values. On-going annual review and revalidation tests will expand the statistics to characterize the variations.

A. USP <643> Total Organic Carbon (TOC)

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A made at different global manufacturing facilities were challenged with 18 Megohm water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 10%, 20%, 30%, 40%, and so on at 10% increment to 200% of the preconditioning flush volume. The samples were then analyzed for total organic carbon.

The TOC data at selected preconditioning flush volume percentages are shown in Table 9a and Figures 6a, 7 and 8. After the minimum required preconditioning flush volume of 54 L/m^2, the extractable TOC levels of all tested Zeta Plus SP media were less than 10 ppm.

Table 9a. TOC of Zeta Plus 60SP, 30SP and 60SP05A Media Extract [ppm]

	Single Layer Media						Dual Layer Media		
	60SP			30SP			60SP05A		
Flush Vol %	# of Lots: 8			# of Lots: 6			# of Lots: 8		
[%]	**Avg**	Max	Min	**Avg**	Max	Min	**Avg**	Max	Min
10%	97.6	21.4	4.0	35.1	94.0	17.0	73.5	125.5	27.0
20%	20.2	11.5	4.2	13.3	21.2	6.8	30.7	50.9	17.2
30%	8.6	6.5	1.8	5.8	9.4	2.2	19.3	36.0	11.1
40%	5.8	4.0	1.2	3.9	6.3	1.3	13.9	27.0	7.4
50%	4.7	4.3	1.0	2.4	4.6	1.0	10.8	19.7	5.1
60%	4.0	4.1	0.9	2.2	3.7	1.1	8.3	14.8	3.7
100%	3.2	1.0	0.8	2.0	3.1	1.0	6.3	9.8	2.8
150%	2.7	0.6	0.8	1.9	2.9	1.0	4.8	7.1	2.2
200%	2.5	0.2	0.8	1.7	2.7	0.8	3.8	5.5	1.8

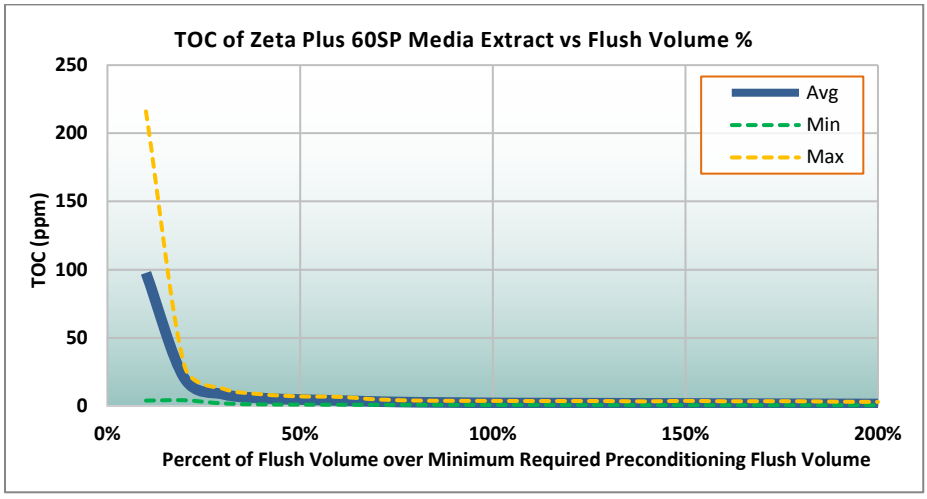


Figure 6a. TOC of Zeta Plus 60SP Media extract

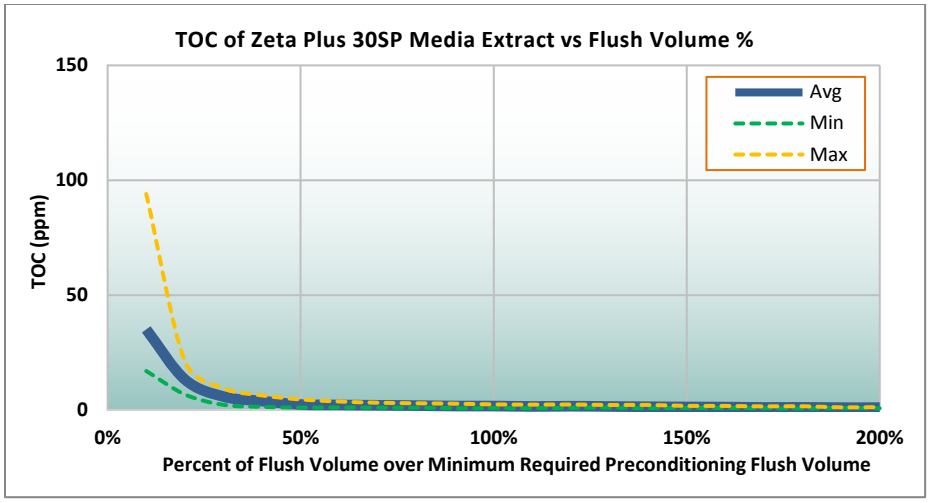


Figure 7. TOC of Zeta Plus 30SP Media extract

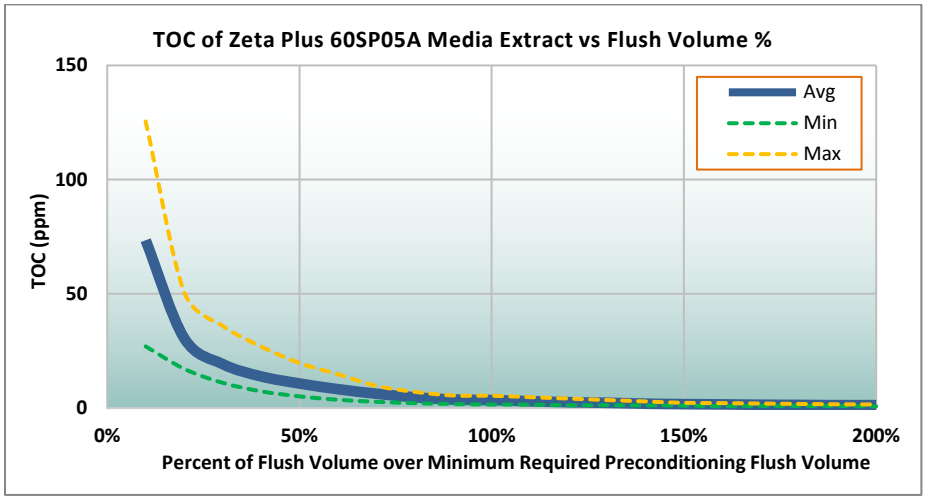


Figure 8. TOC of Zeta Plus 60SP05A Media extract

The 90-mm discs of Zeta Plus media 60SP were also autoclaved at 126 °C for 60 minutes. The previous preconditioning flush sampling and test procedures were followed. The TOC data are shown in Table 9b and Figure 6b. After the minimum required preconditioning flush volume of 54 L/m^2, the extractable TOC levels of all autoclaved Zeta Plus SP media samples were less than 10 ppm.

Table 9b. TOC of Zeta Plus 60SP Media Extract after media autoclave [ppm]			
	Single Layer Media		
	60SP		
Flush Vol %	# of Lots: 8		
[%]	**Avg**	Max	Min
10%	150.3	297.1	45.8
20%	41.6	64.8	18.7
30%	19.9	36.2	7.4
40%	11.1	19.4	4.7
50%	7.8	12.9	3.9
60%	6.1	9.8	3.3
100%	4.8	6.8	2.9
150%	4.0	5.1	2.6
200%	3.4	4.7	2.3

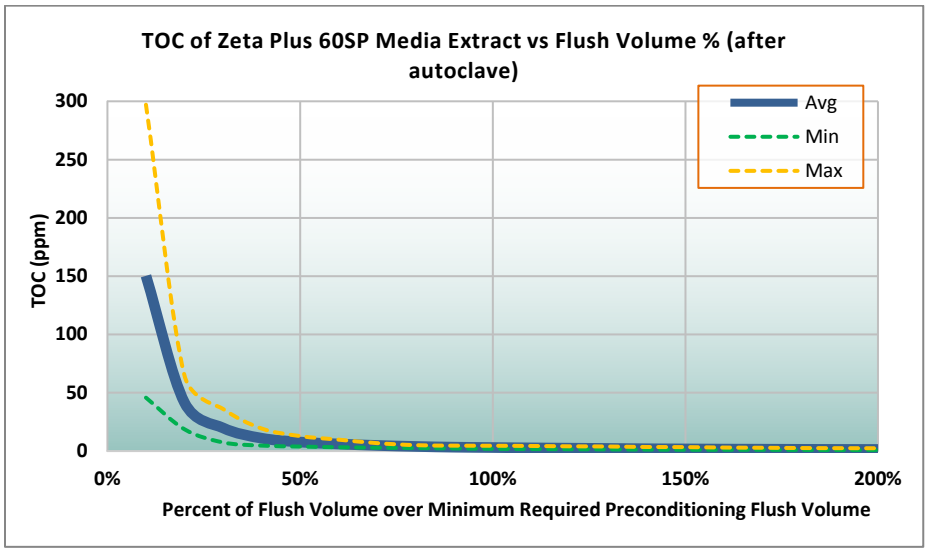


Figure 6b. TOC of Zeta Plus 60SP Media extract after media were autoclaved at 126 ºC for 60 minutes

Reference:
3M SOP: 10L.200.059(ORIG)
Industry Standards: USP <643> Total Organic Carbon
Laboratory Report: Lab-12890, Lab-13006

B. USP <645> Conductivity

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A produced at different global plants were challenged with 18 Megohm water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 10%, 20%, 30%, 40%, and so on at 10% increment to 200% of the minimum required preconditioning flush volume. The samples were then measured for conductivity.

The conductivity data at selected preconditioning flush volume percentages are shown in Table 10 and Figures 9 through 11. The data showed all media extracts had conductivity less than 40 µS/cm after 100% of minimum required preconditioning flush volume and less than 30 µS/cm after 200% flush volume.

The autoclaved Zeta Plus media 60SP samples showed the same trend of conductivity change over flush volume up to two times of minimum required preconditioning flush volume. The conductivity was less than 20 µS/cm after 100% of minimum required preconditioning flush volume and less than 10 µS/cm after 200% flush volume.

Table 10. Conductivity of Zeta Plus 60SP, 30SP and 60SP05A Media Extract [µS/cm]

	Single Layer Media						Dual Layer Media		
	60SP			30SP			60SP05A		
Flush Vol %	# of Lots: 8			# of Lots: 6			# of Lots: 8		
[%]	**Avg**	Max	Min	**Avg**	Max	Min	**Avg**	Max	Min
10%	153.2	262.1	76.9	98.4	197.5	71.9	267.5	505.3	129.6
20%	37.6	52.2	24.0	36.2	44.8	25.5	84.3	110.0	68.2
30%	21.4	29.2	11.4	26.9	35.4	16.9	53.4	70.2	41.1
40%	14.9	22.6	8.6	22.0	29.1	12.0	38.1	51.4	27.1
50%	11.9	17.3	7.2	18.2	22.5	10.3	32.8	45.6	23.0
60%	9.9	15.0	6.3	14.7	17.3	9.5	28.2	37.9	19.7
100%	8.8	12.9	5.6	11.9	15.9	8.5	24.0	32.2	17.4
150%	7.6	9.9	4.9	10.2	14.9	7.4	20.6	26.8	15.8
200%	7.2	9.3	4.3	9.0	13.4	6.3	17.7	21.6	14.6

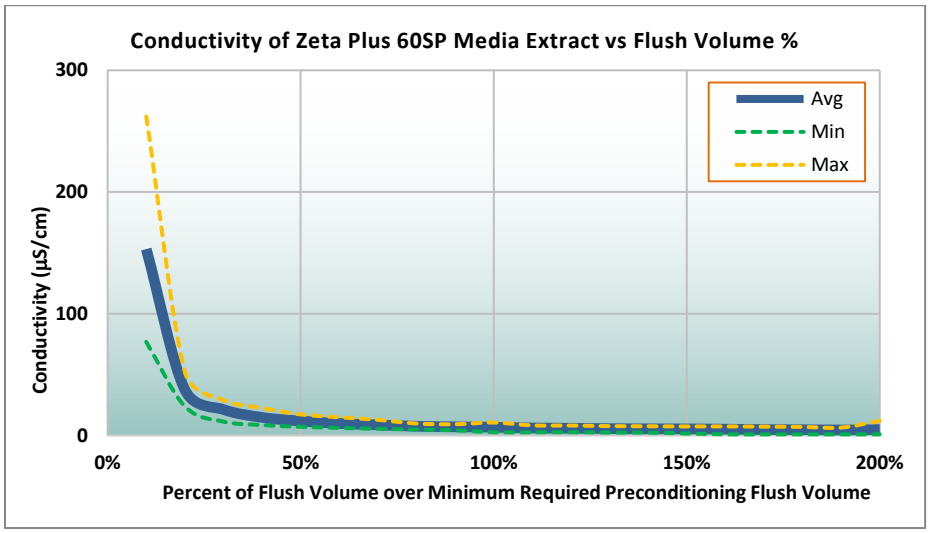


Figure 9. Conductivity of Zeta Plus 60SP media extract

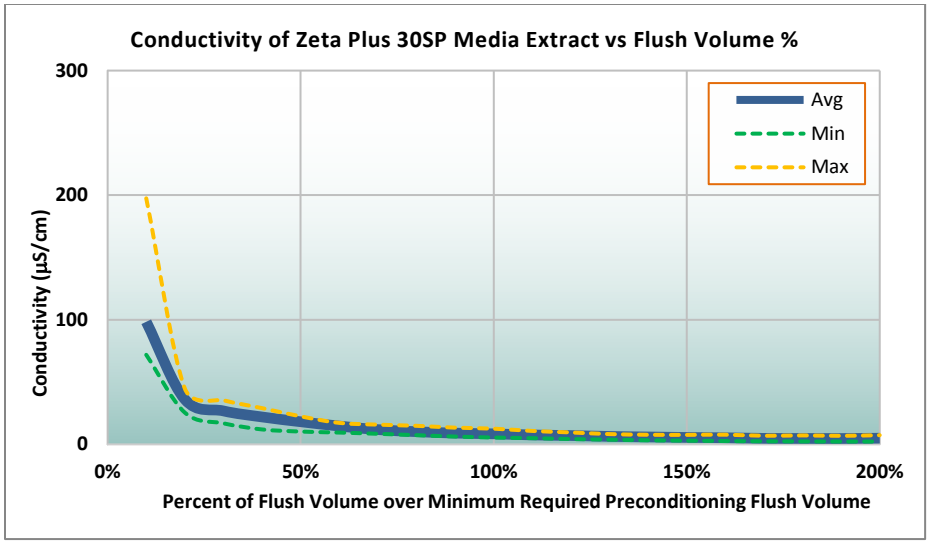


Figure 10. Conductivity of Zeta Plus 30SP media extract

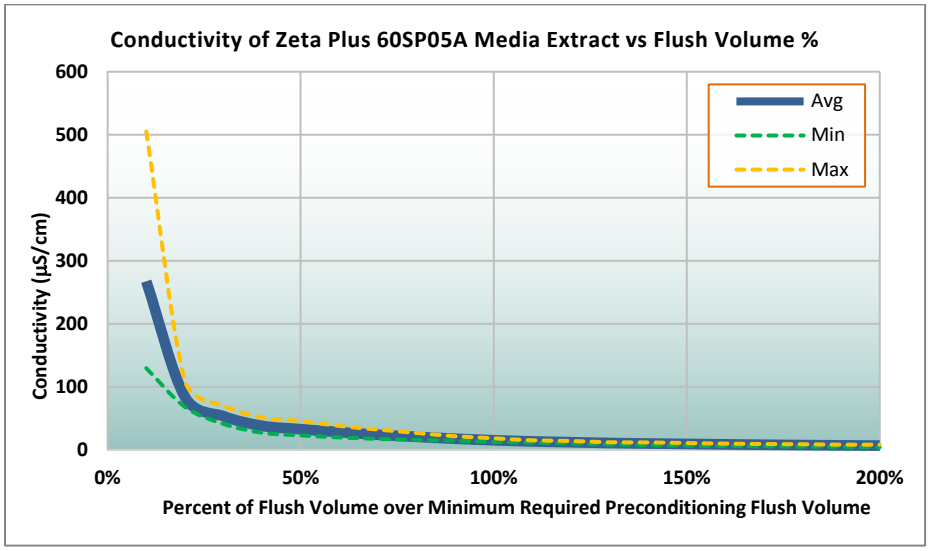


Figure 11. Conductivity of Zeta Plus 60SP05A media extract

Reference:
3M SOP: 10L.200.059(ORIG)
Industry Standards: USP <645> Water Conductivity
Laboratory Report: Lab-12890, Lab-13004

C. USP <791> pH

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A produced at different global plants were challenged with 18 Megohm water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 10%, 20%, 30%, 40%, and so on at 10% increment to 200% of the minimum required preconditioning flush volume. The samples were then measured for pH.

The extract pH at selected preconditioning flush volume percentages, along with pH of DI water controls are shown in Table 11 and Figures 12 through 14. The data showed all media extracts had the pH in the range of 4.5 to 6.4 after 100% of minimum required preconditioning flush volume and in the range of 4.5 to 6.2 after 200% flush volume.

The autoclaved Zeta Plus media 60SP samples showed the same trend of pH over preconditioning flush volume and had pH between 5 and 6.2 after 100% of minimum required preconditioning flush volume.

Table 11. pH of Zeta Plus 60SP, 30SP and 60SP05A Media Extract

	Single Layer Media						Dual Layer Media		
	60SP			30SP			60SP05A		
Flush Vol %	# of Lots: 8			# of Lots: 6			# of Lots: 8		
DI Water Control	**6.3**	7.3	5.3	**6.2**	6.6	5.6	**6.3**	6.6	5.7
[%]	**Avg**	Max	Min	**Avg**	Max	Min	**Avg**	Max	Min
10%	6.0	6.7	4.4	5.0	5.5	4.4	5.6	6.8	4.8
20%	5.5	6.5	4.4	4.8	5.4	4.3	5.6	6.6	4.8
30%	5.2	6.4	4.3	4.6	5.2	4.3	5.4	6.5	4.8
40%	5.1	6.1	4.3	4.6	5.2	4.4	5.3	6.5	4.6
50%	5.1	6.1	4.2	4.7	5.2	4.5	5.2	6.4	4.5
60%	5.1	6.0	4.3	4.7	5.2	4.6	5.2	6.4	4.5
100%	5.1	5.9	4.5	4.9	5.2	4.7	5.2	6.4	4.5
150%	5.1	5.9	4.5	4.9	5.2	4.6	5.2	6.3	4.6
200%	5.1	6.0	4.5	5.0	5.2	4.7	5.2	6.2	4.6

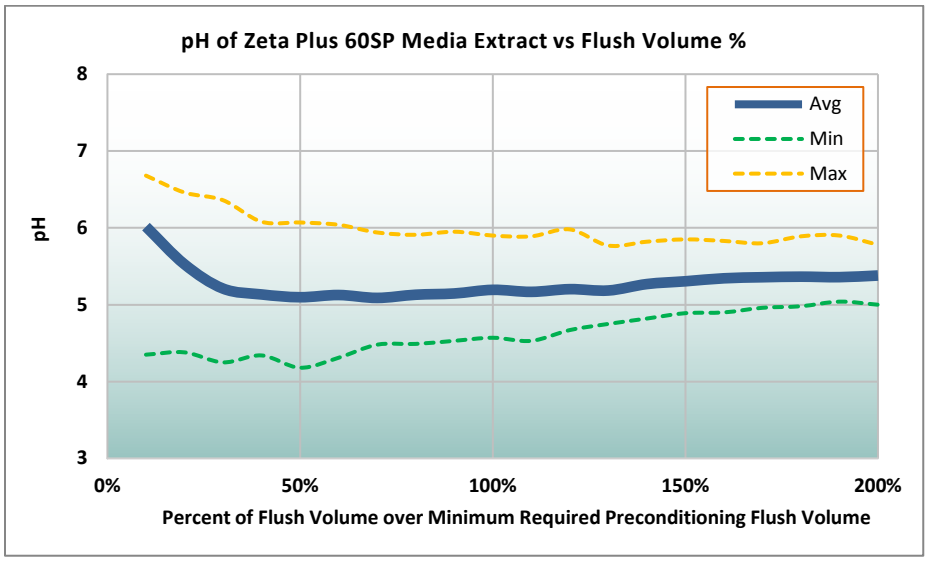


Figure 12. pH of Zeta Plus 60SP Media Extract over Flush Volume

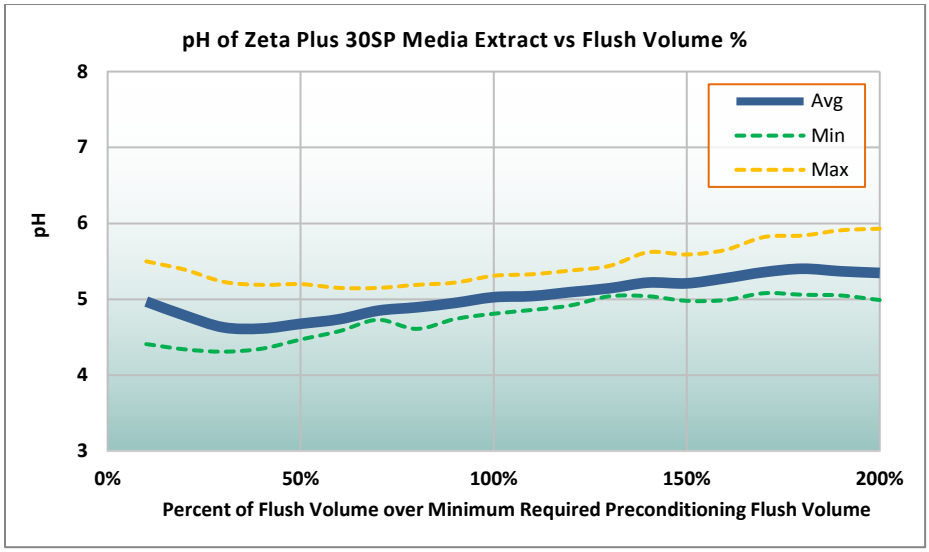


Figure 13. pH of Zeta Plus 30SP Media Extract over Flush Volume

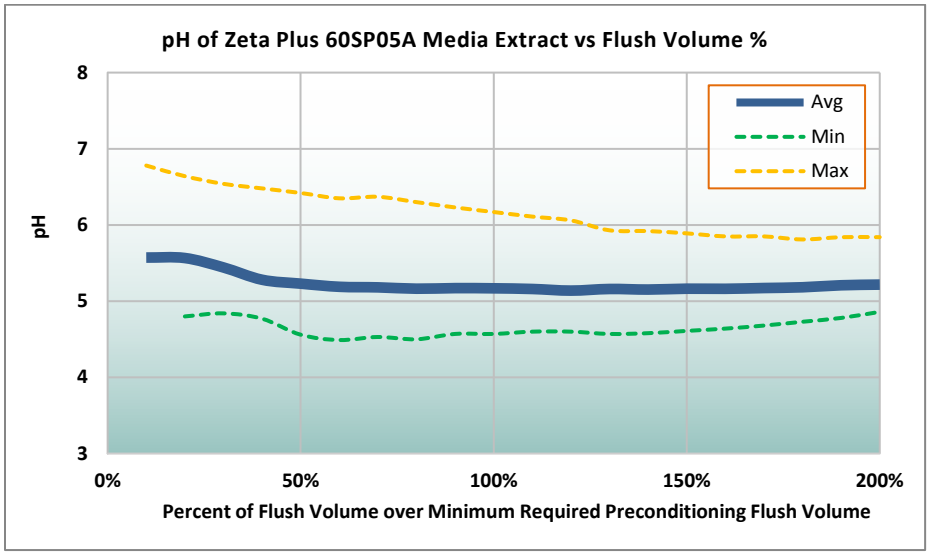


Figure 14. pH of Zeta Plus 60SP05A Media Extract over Flush Volume

Reference:
3M SOP: 10L.200.059(ORIG)
Industry Standards: USP <791> Water pH
Laboratory Report: Lab-12890, Lab-13004

D. Non-Volatile Residues (NVR)

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A produced at different global plants were challenged with 18 Megohm water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 34%, 66%, 100%, and 200% of the preconditioning volume. The same media disc were then soaked in DI water for one hour and this liquid sample was analyzed. These extract samples were taken to dryness under controlled conditions until weighing vessels of constant final weights were observed.

Table 12. Non-Volatile Residues (NVR) of Zeta Plus Media 60SP and 60SP05A Extract [mg/L]

	Single Layer Media			Dual Layer Media		
	60SP			60SP05A		
Flush Vol %	# of Lots: 5			# of Lots: 4		
[%]	**Avg**	Max	Min	**Avg**	Max	Min
34%	149	180	93	193	239	147
68%	19	24	12	17	20	14
100%	8	10	5	9	10	8
200%	4	4	4	4	4	4
1 Hour Static Soak	11	13	7	13	16	11

Reference:
3M SOP: 10L.200.013(D)
Laboratory Report: Lab-12836

E. USP <232>/<233> and ICH Q3D Elemental Impurities

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A produced at different global plants were challenged with 18 Megohm DI water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 10%, 20%, 30%, 40%, and so on at 10% increment to 200% of the preconditioning flush volume. The 10%, 100% and 200% extract samples were then analyzed.

In this sub-section the symbol "<LOQ" in Table 13 represents value lower than Limit of Quantification (LOQ).

Table 13 - Extractable Elemental Impurities of Zeta Plus Media 60SP, 30SP and 60SP05A Extract [ppb]

			Single Layer Media						Dual Layer Media		
ICH Class	Element	LOQ [ppb]	60SP Max. of 8 lots			30SP Max. of 6 lots			60SP05A Max. of 8 lots		
At % of Flush Volume			10%	100%	200%	10%	100%	200%	10%	100%	200%
1	As	16.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Pb	0.013	0.42	0.22	0.30	0.94	0.22	1.2	0.59	0.23	0.22
	Cd	7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Hg	1.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
2A	V	0.003	116	15	15	1.9	0	0	102	13	33
	Ni	0.027	<LOQ	<LOQ	<LOQ	4.8	0.95	3.8	12	0.41	0.1
	Co	0.007	0.90	0.20	0.19	0.32	0.25	0.18	0.94	0.21	0.20
2B	Ag	1.0	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Au	7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Tl	0.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Pd	7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Pt	0.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Ir	0.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Os	2.0	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Rh	0.7	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Ru	0.3	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	Se	0.27	0.95	0.26	0.16	2.9	1.7	0.18	1.9	0.7	0.16
3	Sb	0.007	1.7	1.1	0.16	0.65	0.65	0.09	1.46	0.22	0.16
	Ba	0.013	69	2	16	46	3.8	11	80	7.1	24
	Li	0.03	12	0.52	2.05	3	0.13	4.4	12	0.66	2.9
	Cr	0.013	2.2	0.08	0.05	0.6	0.05	0.45	2.0	0.09	0.50
	Cu	0.07	22	0.58	1.01	4.9	0.64	0.34	18	1.2	0.31
	Mo	0.03	65	5.8	8.3	6.4	0.13	0.11	48	5.5	12
	Sn	0.013	0.21	0.18	0.14	0.17	0.14	8.9	0.22	0.16	63
Other Elements	B	2.3	76	<LOQ	<LOQ	3.9	<LOQ	<LOQ	26	<LOQ	<LOQ
	Fe	0.007	579	20	12	228	3	2	567	29	12
	Zn	0.3	41	33	15	47	18	18	50	22	18
	K	0.23	2267	124	76	1471	111	55	2678	435	158
	Ca	0.7	2297	55	36	2356	87	50	4923	283	76
	Na	0.10	10507	369	212	5753	287	225	14497	1093	374
	Mn	0.007	78	3.1	2	32	1.4	0.8	113	6.8	2.2
	Mg	0.027	1171	23	14	726	28	16	2218	92	20
	W	0.13	1.17	0.16	0.15	0.18	0.28	0.13	0.91	1.1	0.14
	Al	0.17	840	27	14	273	10	8.0	1066	36	14

Reference:
Industry Standard: USP <232> Elemental Impurities – Limits; USP <233> Elemental Impurities – Procedure; ICH Guideline for Elemental Impurities Q3D, Dec 2014
Laboratory Report: Lab-12892, Lab-13004

F. USP <788> Particulate Matter in Injections

The 90-mm discs of Zeta Plus media 60SP, 30SP and 60SP05A produced at different global plants were challenged with 18 Megohm water (25°C) at a constant flux of 1200 LMH to a total volume of two times of minimum required preconditioning flush volume of 54 L/m^2. Filtrate samples were collected at 33%, 66%, 100%, 150% and 200% of the preconditioning flush volume. Media discs were then soaked in DI water for one hour. The extract samples were analyzed for Particulate Matter.

The particle counts in the size ranges of 10-25 and >=25 micron are shown in Table 14. The tests showed that minimum required preconditioning flush of the Zeta Plus SP filter media reduced the particulate matter of effluent.

Table 14. Particulate Matter (Average Cumulative Counts per ml - Control Corrected) [#/mL]

	Single Layer Media						Dual Layer Media					
	60SP						60SP05A					
	# of Lots: 7						# of Lots: 6					
Flush Vol %	> 10 microns			> 25 microns			> 10 microns			> 25 microns		
[%]	**Avg**	Max	Min	**Avg**	Max	Min	Avg	Max	Min	**Avg**	Max	Min
34%	178	278	29	11	18	6	609	1099	198	28	66	7
68%	53	117	29	6	15	1	68	88	54	3	5	2
100%	51	69	40	7	17	2	56	83	39	2	3	2
200%	22	50	9	7	27	1	17	26	4	1	1	1
1 Hour Static Soak	39	63	28	5	9	2	157	273	42	6	10	3

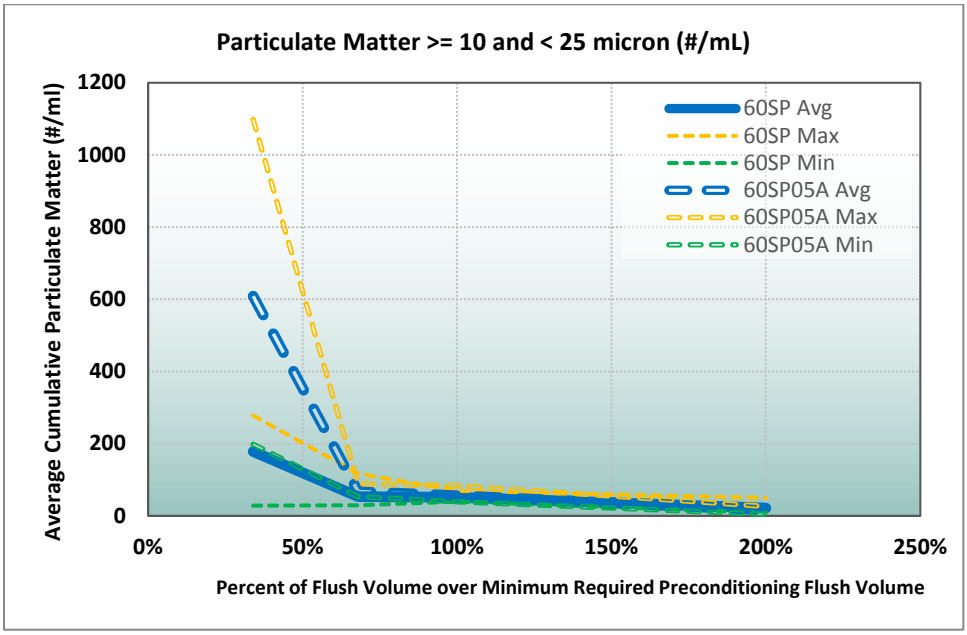


Figure 15. Particulate Matter of 10-25 micron in Zeta Plus 60SP and 60SP05A Media Extract

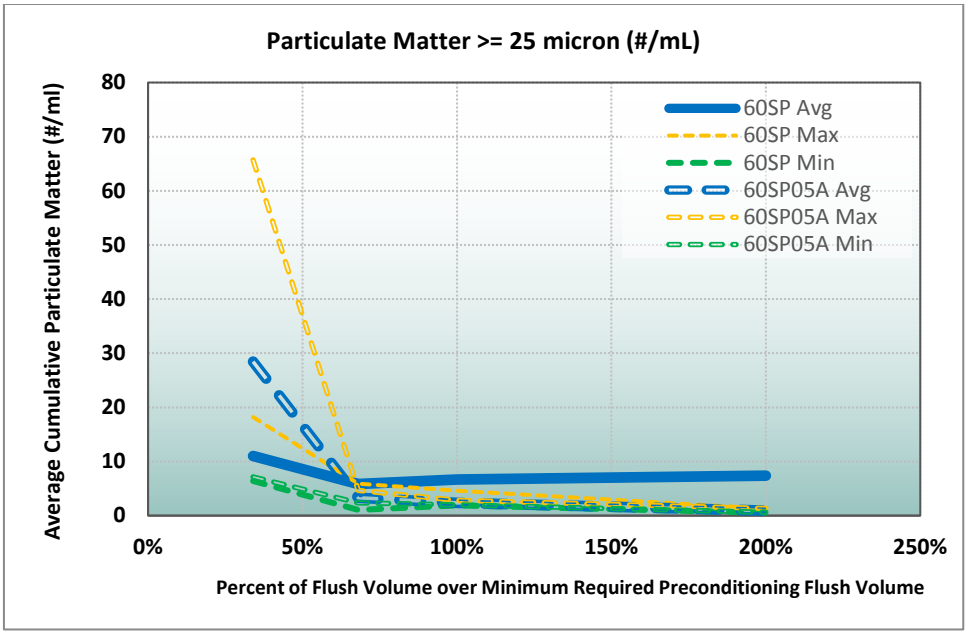


Figure 16. Particulate Matter of >=25 micron in Zeta Plus 60SP and 60SP05A Media Extract

Reference:
3M SOPs: 10L.300.016(A)
Industry Standards: USP <788> Particulate Matter in Injections
Laboratory Report: Lab-12836, Lab-13007

G. USP <85> Bacterial Endotoxin

The 47-mm discs of Zeta Plus media 60SP and 60SP05A produced at different global plants were challenged with Sterile Water for Injection (SWFI) at a constant flux of 900 LMH to a total volume of 100% of the minimum required preconditioning volume. The filtrate samples collected at the end of flush were analyzed for the test of extractable endotoxin concentration by LAL reactivity method.

The Zeta Plus SP filter media tested met the bacterial endotoxin limits for PFW/WFI of ≤ 0.25 EU/mL, as shown in Table 15.

Table 15 - Extractable Endotoxin of Zeta Plus 60SP and 60SP05A Media

		Single Layer Media	Dual Layer Media
		60SP	60SP05A
		# of Lots: 8	# of Lots: 5
Extract Solution	SWFI, pH 5.5	**Max**	**Max**
Extractable Endotoxin	[EU/mL]	<0.01	<0.01
Acceptance	[EU/mL]	<0.25	<0.25

Reference:
3M SOPs: 10L.500.006(F); 10L.500.012(ORIG)
Industry Standards: USP <85> Bacterial Endotoxin
Laboratory Report: Lab-12837
Manufacturing Quality Database

H. USP <661> Containers - Plastics

The wetted surface area of each Zeta Plus™ filter component can be used to calculate the expected residue concentration in a composite product extract. Samples of resin used to make the various molded components were made into 7.5 x 2.0 x 0.2 cm plaques. The extraction conditions described in USP <661> for polypropylene were followed for all components. The non-volatile residues from water, n-propanol (at 70°C), and hexanes (at 50°C) were determined and listed in Table 16 as mg of residue per cm² of surface area extracted. The "--" symbol in this table indicates data is currently not available.

Table 16 - Extract Residue of Filter Components per USP <661> Methodology

Part	Material of Construction	Extract Residue [mg/cm²]		
		Water	1-Propanol	Hexanes
Cartridges				
Separator	Polypropylene	0.005	0.104	0.826
Separator	Mineral-filled Polypropylene	0.016	0.028	0.227
Separator	Polypropylene	0.002	0.039	0.698
Netting	Polypropylene	0.001	0.043	0.423
Edge Seal (Single Layer)	Polypropylene	0.005	0.104	0.826
Edge Seal (Single Layer)	Mineral-filled Polypropylene	0.016	0.028	0.227
Edge Seal (Single Layer)	Polypropylene	0.011	0.024	0.173
Edge Seal (Single Layer)	Polypropylene with pigment	0.020	0.036	0.257
Edge Seal (Single Layer)	Mineral-filled Polypropylene	--	--	--
Edge Seal (Dual Layer)	Thermoplastic Elastomer	0.003	12.6	25.4
Edge Seal (Dual Layer)	Thermoplastic Elastomer	<0.001	10.1	17.6
Ring Seal	Polypropylene	0.005	0.104	0.826
Ring Seal	Polypropylene	0.002	0.039	0.698
Gasket Retainers	Polypropylene	0.005	0.104	0.826
Gasket Retainers	Mineral-filled Polypropylene	0.016	0.028	0.227
Gasket Retainers	Polypropylene	0.002	0.039	0.698
8" Plug-in Unitizing Post	Polypropylene	0.005	0.104	0.826
Laboratory Capsules				
Shells (Inlet and Outlet)	Polypropylene	0.005	0.104	0.826
Ring Seal (dual layer media)	Polypropylene	0.005	0.104	0.826
Luer cap & luer-barb connector	Polypropylene	--	--	--
Scale-up Capsules				
Separators	Polypropylene	0.005	0.104	0.826
Spacer for E1020	Polypropylene	0.005	0.104	0.826
Flow Inhibitor Disc for E0170	Polypropylene	0.005	0.104	0.826
Edge Seal	Thermoplastic Elastomer	0.003	12.6	25.4
Edge Seal	Thermoplastic Elastomer	<0.001	10.1	17.6
Inner Seal	Thermoplastic Elastomer	0.003	12.6	25.4
Inner Seal	Thermoplastic Elastomer	<0.001	10.1	17.6
Endcap	Thermoplastic Elastomer	0.003	12.6	25.4
Endcap	Thermoplastic Elastomer	<0.001	10.1	17.6
Shells	Polysulfone	--	--	--
Back-up O-ring	Polypropylene	0.005	0.104	0.826
Production Capsules				
Separator	Polypropylene	0.005	0.104	0.826
Spacer	Polypropylene	<0.005	0.079	1.06
Edge Seal	Thermoplastic Elastomer	0.003	12.6	25.4
Edge Seal	Thermoplastic Elastomer	<0.001	10.1	17.6
Ring Seal	Thermoplastic Elastomer	0.003	12.6	25.4
Ring Seal	Thermoplastic Elastomer	<0.001	10.1	17.6
Male & Female Connectors	Polypropylene	0.005	0.104	0.826
Shell 1	Polycarbonate	<0.002	0.003	<0.004
Shell 2	Polyphenylene Oxide/Polystyrene	<0.002	0.036	0.004
Manifold 1	Polycarbonate	<0.002	0.003	<0.004
Manifold 2	Polyphenylene Oxide/Polystyrene	<0.002	0.036	0.004

Reference:
Industry Standards: USP <661> Containers – Plastics, Rev. 38
Laboratory Reports: Lab-12720, Lab-12788, Lab-12798, Lab-12946

IX. Media Shelf Life

A study was performed on various grades of Zeta Plus media stored in the original package in a non-air-conditioned warehouse environment. The QC release tests were completed on selected aged media including Pressure Drop at constant air flow, Wet Tensile Strength, Calcium Extraction, Iron Extraction, Color Extraction and Endotoxin Extraction. Test data were then compared to QC release specifications and the initial test results.

The aged SP media performance met the release specifications. Based on that, with a safety factor considered, a 5 year shelf life claim is made for Zeta Plus SP Series filter media.

To account for extreme conditions that Zeta Plus media may be exposed to during shipping, an accelerated aging study was initiated and is on-going. Contact 3M for more information.

All Zeta Plus media products should be stored in the original package and in a controlled environment. The best long term storage conditions are where the average temperature is between 5 and 30°C with short term excursion to 50°C, and the relative humidity is less than 90%. Lower temperatures and controlled humidity will have less degrading effects on these products.

All Zeta Plus™ products and Manifolds should be inspected before use to determine if any unanticipated damage has occurred during shipping and storage. This includes an inspection of the O-rings to confirm that they have no nicks or cuts, become cracked, exhibited a loss of elasticity, that would prevent a normal sealing operation.

References:
Laboratory Reports: SASS-1246

X. Regulatory Compliance

A. USP <88> Class VI Biological Reactivity Test, *In Vivo*

The USP <88> VI Biological Reactivity Tests, *In Vivo* were performed on media and other components of the Zeta Plus™ SP Series filter products. The tests were performed by an accredited and independent laboratory following GLP. The test is based on 4 grams of media, at an extracting ratio of 5ml of fluid per gram.

The compliance of the Zeta Plus SP Series filter components to the USP <88> Class VI requirements established in the reported USP revision are included in the Drug Master File and can be made available upon request.

The USP Biological Reactivity Tests are completed on a single grade of SP family from each global manufacturing facility. Zeta Plus media grade 60SP was selected as a representative grade of SP Series media for Biological Reactivity tests. The selection is based on media compositions and internal Biological Reactivity test results of various grades within SP Series media family.

B. BSE/TSE

3M understands the continued public interest and the increased regulatory scrutiny concerning the transmission of bovine spongiform encephalopathy (BSE) and other transmissible spongiform encephalopathies (TSE). In order to address these issues, the following statement is offered: In order to assess the BSE/TSE risk associated with the above products, we have contacted our suppliers of raw materials and performed an evaluation of our production processes to determine if any of the materials used are of animal origin. The result of our survey and inquiries of our raw material suppliers has revealed that the polypropylene resins used to mold parts and the thermoplastic elastomer used in edge seals may contain tallow derivatives and certain elastomer gaskets could contain a stearic acid that is used as an activator in the vulcanization process. We can state, however, that our suppliers have indicated that these parts which use tallow derivatives and stearic acid are processed at conditions conforming to the requirements of the European Medicines Agency note for guidance EMEA/410/01 rev.3.

XI. Quality Assurance

Pharmaceutical and Biological products manufacturers routinely visit 3M manufacturing sites to audit production quality management systems and documentation. The full ISO 9001:2008 certifications for 3M Separation and Purification Sciences Division global plants are available on request.

The Zeta Plus™ SP Series filter products are released with Certificate of Quality (COQ).

The Zeta Plus SP Series filter products are defined as non-hazardous articles under REACH and do not require a Safety Data Sheet under Article 31 of Regulation (EC) No. 1907/2006.

These products are not regulated under the OSHA Hazard Communication Standard (CFR Title 29 1910.1200). An Article Information Sheet is not required for these products.

Article Information Sheets are available in the US as courtesy.

Product Use

Intended uses: Manufacturing of pharmaceutical (drug) products, including active pharmaceutical ingredients and vaccines.

Prohibited uses: As a component in a medical device that is regulated by any agency, and/or globally exemplary agencies, including but not limited to: a) FDA, b) European Medical Device Directive (MDD), c) Japan Pharmaceuticals and Medical Devices Agency (PMDA); Applications involving permanent implantation into the body; Life-sustaining medical applications; Applications requiring FDA Food Contact compliance without use restrictions

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