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3M Separation and Purification Sciences Division

# 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP 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, has operations in more than 65 countries. Facilities that participate in the manufacturing of 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products as shown below, have quality systems registered to quality system standards as noted below.

| Stafford Springs, CT, USA | Mazeres, France | Wroclaw, Poland |
|---|---|---|
| Registered to:<br>ISO 9001 | Registered to:<br>ISO 9001 | Registered to:<br>ISO 9001 |

This Regulatory Support File provides information pertinent to the 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products. Contained herein are detailed test methods, product specifications, product performance information and regulatory documentation related to pharmaceutical and biologics manufacturing processes. 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 routinely completes a thorough review of the USP and ICH standards and this regulatory support file to ensure that the claims and data package are current.

Complementary product information, use and operating instructions and guidelines, and technical data can be found in the 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter product literature and product quality certifications. Further information can be obtained by contacting your local 3M representative.

The intended use(s), restrictions on use, and production selection and use for 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products are stated below.

**Intended Use(s)**: 3M™ Zeta Plus™ single-use filter products are intended for use in biopharmaceutical processing applications of aqueous and chemical based pharmaceuticals (drugs) and vaccines in accordance with the product instructions and specifications, and cGMP requirements, where applicable.

Since there are many factors that can affect a product's use, the customer and user remain responsible for determining whether the 3M product is suitable and appropriate for the user's specific application, including user conducting an appropriate risk assessment and evaluating the 3M product in user's application.

**Restrictions on Use**: 3M advises against the use of these 3M products in any application other than the stated intended use(s), since other applications have not been evaluated by 3M and may result in an unsafe or unintended condition. Do not use in any manner whereby the 3M product, or any leachable from the 3M product, may become part of or remains 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 Regulation (MDR), c) Japan Pharmaceuticals and Medical Devices Agency (PMDA) or in applications involving permanent implantation into the body; Life-sustaining medical applications; Applications requiring food contact compliance.

**Product Selection and Use**: Many factors beyond 3M's control and uniquely within user's knowledge and control can affect the use and performance of a 3M product in a particular application. As a result, end-user is solely responsible for evaluating the product and determining whether it is appropriate and suitable for end-user's application, including completing a risk assessment that considers the product leachable characteristics and its impact on drug safety, conducting a workplace hazard assessment and reviewing all applicable regulations and standards (e.g., OSHA, ANSI, etc.). Failure to properly evaluate, select, and use a 3M product and appropriate safety products, or to meet all applicable safety regulations, may result in injury, sickness, death, and/or harm to property.

## II. Drug Master File Reference

3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filters are listed in a Drug Master File (DMF) registered with the United States Food and Drug Administration (FDA).

The information contained in the DMF 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 DMF 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 Purification Inc. must provide a letter of authorization permitting FDA to reference the DMF. The applicant is required to include a copy of the letter of authorization in their application. Contact 3M Separation and Purification Sciences Division to initiate a review of the DMF. 3M will update this Regulatory Support File as a routine aspect of product maintenance.

## III. Product Descriptions

3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products are a family of advanced depth filters designed for optimal clarification of various bioprocess, biological and pharmaceutical fluids. 3M™ Zeta Plus™ 01AP filter media contains a mixture of cellulose and a melamine formaldehyde crosslinking binder resin and 3M™ Zeta Plus™ CP Series filter media contain a mixture of inorganic filter aids, cellulose and a melamine formaldehyde crosslinking binder resin. They offer a combination of mechanical and electrokinetic particulate removal mechanisms with an intermediate charge level relative to other 3M™ Zeta Plus™ filter media offerings.

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

3M has global manufacturing and supply chain capabilities. The products described below may be produced at multiple global locations. 3M assigns a unique ID number to each product specific to its country of origin and will ensure lot traceability to each manufacturing facility. Note that special configurations for current customers may not be covered by this RSF.

8” Diameter Cartridges

| Table 1. 8” Cartridge Product Descriptions: Single Layer Media | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Manufacturing Facility** | **Product Description Examples: 4510922 60CP, 4516703 50CP, Z8FA2NPA60CP, Z08DA01CP** | | | | | | |
| United States | **Diameter Designation** | | | | **Gasket Material** | | **Grade** |
| | 45109 - 8 cell | | | | 13 – Fluorocarbon (FPM)<br>22 – Silicone (VMQ) | | 10CP<br>30CP<br>50CP<br>60CP<br>70CP |
| | 45167 - 7 cell Plug-in | | | | 03- Fluorocarbon (FPM)<br>04- Silicone (VMQ) | | |
| | **Diameter Designation** | **Number of Cells** | **Configuration** | **Material** | **Gasket Material** | **Package** | **Grade** |
| | Z8FA -Plug-in | 2 - 2 cell<br>4 - 4 cell | N - None | P - Polypropylene | A – Silicone (VMQ)<br>B – Fluorocarbon (FPM) | 2 - Standard | 10CP<br>30CP<br>50CP<br>60CP<br>70CP |
| France | **Diameter Designation** | | **Number of Cells** | | **Gasket Material** | | **Grade** |
| | Z08 | | D – 8 cell | | A – Silicone (VMQ)<br>B – Fluorocarbon (FPM) | | 01CP<br>10CP<br>30CP<br>50CP<br>60CP<br>70CP |

12” Diameter Cartridges

| Table 2. 12” Cartridge Product Descriptions: Single Layer Media | | | | |
|---|---|---|---|---|
| **Manufacturing Facility** | **Product Description Examples: 4511303 01AP, 4511517 10CP, 4524501A50CP** | | | |
| United States | **Diameter Designation** | **O-Ring Material** | | **Grade** |
| | 45113 – 18 cell | 03 - Fluorocarbon (FPM)<br>11 – Silicone (VMQ) | | 01AP |
| | **Diameter Designation** | **O-Ring Material** | | **Grade** |
| | 45115 – 16 cell<br>45116 – 9 cell | 14 - Fluorocarbon (FPM)<br>17 – Silicone (VMQ) | | 10CP<br>30CP<br>50CP<br>60CP<br>70CP |
| | **Diameter Designation** | **Material** | **O-Ring Material** | **Grade** |
| | 45245 – 16 cell | 01 - Polypropylene (PP) | A – Silicone (VMQ)<br>B – Fluorocarbon (FPM) | 50CP |

16” Diameter Cartridges

| Table 3. 16” Cartridge Product Descriptions: Single Layer Media | | | | |
|---|---|---|---|---|
| **Manufacturing Facility** | **Product Description Examples: Z16PA70CP** | | | |
| United States | **Diameter Designation** | **Configuration** | **Gasket Material** | **Grade** |
| | Z16 | P - 14 cell<br>H - 16 cell | A – Silicone (VMQ)<br>B – Fluorocarbon (FPM) | 01AP<br>30CP<br>50CP |
| France | **Diameter Designation** | **Configuration** | **Gasket Material** | **Grade** |
| | Z16 | M – 14 cell, FR height<br>P - 14 cell, US height<br>D - 15 cell<br>S - 9 cell | A – Silicone (VMQ)<br>B – Fluorocarbon (FPM) | 01AP<br>01CP<br>10CP<br>30CP<br>50CP<br>70CP |

Laboratory Capsules

| Table 4. Laboratory Capsule Product Descriptions: Single Layer Media | | | |
|---|---|---|---|
| | | | |
| **Manufacturing Facility** | **Product Description Example: BC0025L70CP** | | |
| United States | **Diameter Designation** | **Configuration** | **Grade** |
| | BC0025 | L - Luer<br>S - Sanitary | 01AP<br>10CP<br>30CP<br>50CP<br>60CP<br>70CP |

## IV. Product Design

All components used in the manufacture of 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series 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 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter media are composed of the same materials of construction at varying ratios. Therefore, the test results reported herein are generally applicable to all grades and product configurations.

3M™ Zeta Plus™ products containing 01AP or CP media are produced in the United States, France and Poland. Raw materials are purchased consistent with global specifications.

### A. Media

3M™ Zeta Plus™ 01AP filter media contains a mixture of cellulose and a melamine formaldehyde crosslinking binder resin and 3M™ Zeta Plus™ CP Series filter media contain a mixture of inorganic filter aids, cellulose and a melamine formaldehyde crosslinking binder resin. They offer a combination of mechanical and electrokinetic particulate removal mechanisms with an intermediate charge level relative to other 3M™ Zeta Plus™ filter media offerings. The media is produced by a wetlaid process.

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

## 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 binder bands. Netting is added to selected model numbers to maintain flow path between lenticles. Each cartridge has two gaskets one at the top and one at the bottom. Depending on the cartridge configuration, three standard gasket materials may be offered: silicone (VMQ), fluorocarbon (FPM) or 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.

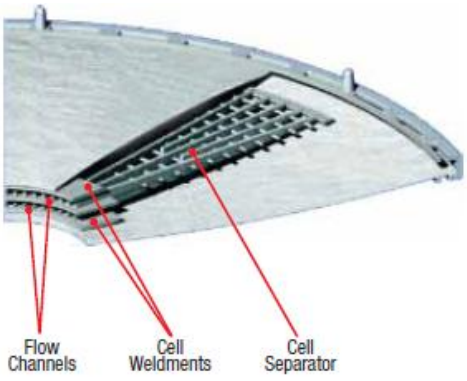


Figure 1a. 3M™ Zeta Plus™ cartridge lenticle configuration with single media layer

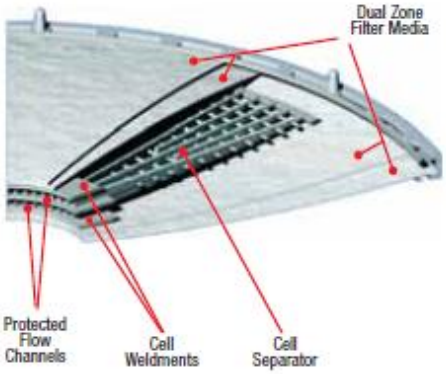


Figure 1b. 3M™ Zeta Plus™ cartridge lenticle configuration with dual media layers

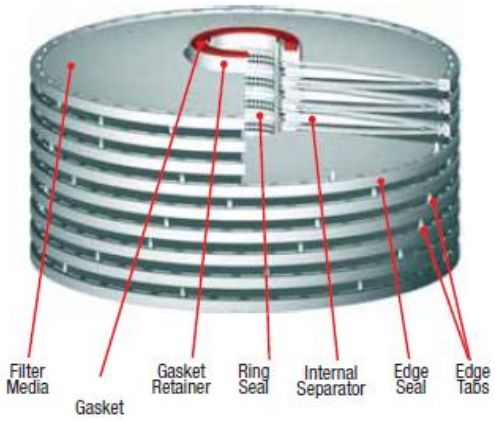


Figure 1c. 3M™ Zeta Plus™ cartridge and components

Figure 1d. 3M™ Zeta Plus™ cartridges shown with housings

Figure 1e. 3M™ Zeta Plus™ 8” plug-in cartridge

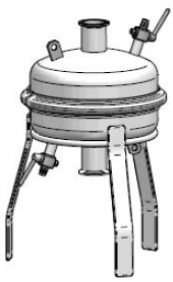

Figure 1f. 3M™ Zeta Plus™ plug-in cartridge housing

## C. Capsules

There is one capsule category for the 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP filters: Laboratory Capsules.

The Laboratory capsule (BC0025) is constructed by compressing the single 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 nominal surface area of 25 cm².

### Figure 2. Laboratory Capsules

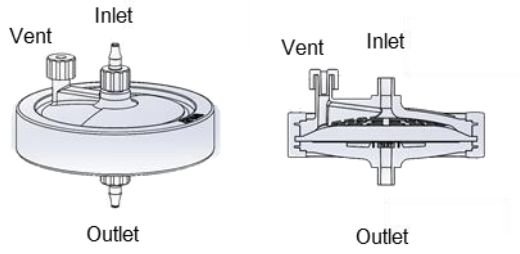


Figure 2a. BC0025 Capsule – Luer Style

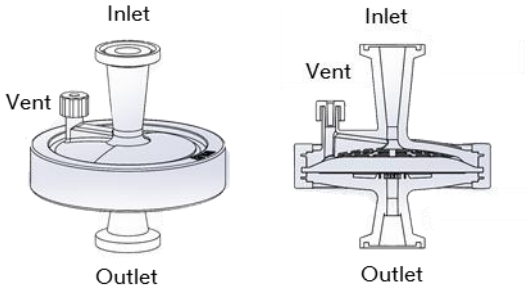


Figure 2b. BC0025 Capsule – Sanitary Style

## D. Materials of Construction

| Table 5. Materials of Construction – Filter Cartridges | |
|---|---|
| **Part Type** | **Materials** |
| 3M™ Zeta Plus™ 01AP Filter Media | Cellulose, Binding Resin |
| 3M™ Zeta Plus™ CP Filter Media | Natural Filter Aids, Cellulose, Binding Resin |
| Retainers and separators | Polypropylene or Mineral-filled Polypropylene |
| Netting[1] | Polypropylene |
| Edge Seal | Polypropylene or Mineral-filled Polypropylene |
| Ring Seal | Polypropylene |
| Binder bands | 316 stainless steel or Hastelloy® |
| Gaskets or O-rings | Silicone or Fluorocarbon |
| 8" Plug-in Unitizing Post | Polypropylene |

1 Specific 12" and 16" cartridges

| Table 6. Materials of Construction – Laboratory Capsule | |
|---|---|
| **Part Type** | **Materials** |
| | **BC0025** |
| Nominal Surface Area | 25 $cm^2$ |
| 3M™ Zeta Plus™ 01AP Filter Media | Cellulose, Binding Resin |
| 3M™ Zeta Plus™ CP Filter Media | Natural Filter Aids, Cellulose, Binding Resin |
| Shells | Polypropylene |
| Ring Seal (dual layer media) | Polypropylene |
| Edge Seal Overmold | Glass Fiber Filled Polypropylene |
| Luer cap & luer-barb connector | Polypropylene |

## E. Capsule Design Characteristics

Weights and Volumes shown in Table 7 below were experimentally determined from samples of various representative grades and families of 3M™ Zeta Plus™ filter media. **Please note that these values are presented for guidance only and are not specifications**; actual amounts depend upon individual capsule variability, exact blow-down conditions, media type in capsule, the number of capsules in the system, the process fluid, and loading level of the capsule.

1) Dry Weight – Weight of capsule prior to use.
2) Wet, Post Blow-down Weight - Liquid retained in the system, as measured by the differential between the capsule dry weight and the capsule weight after blow-down. This predominantly reflects the liquid left in the filter media. Actual amount depends upon exact blow-down conditions, media type in capsule, the number of capsules in the system, the process fluid, and loading level of the capsule.
3) Capsule Fill Volume - Amount of liquid necessary to fill the capsule from inlet to outlet, including media, calculated using the filled capsule weight and flush fluid density.
4) Post Blow-down Hold-Up Volume - Estimated volume of residual preconditioning flush liquid after air/gas blow-down using water as the flush fluid, and calculated by post-blow-down weight and flush fluid density. Actual amount depends upon exact blow-down conditions, media type in capsule, the number of capsules in the system, the process fluid, and loading level of the capsule.

**Table 7. Capsule Design Characteristics – Laboratory Capsules**

| **Product Name** | **BC25, Luer** | **BC25, Sanitary** |
|---|---|---|
| Nominal Surface Area | 25 cm² | 25 cm² |
| Inlet/Outlet | Luer | ½" - ¾" Sanitary Style |
| **Nominal Dimensions** | | |
| Single Layer (height by diameter) | 6.5 cm x 7.6 cm (2.6 inches x 3 inches) | 7.9 cm x 7.6 cm (3.1 inches x 3 inches) |
| **Weight** | | |
| Dry – Single Layer | ≈ 60 g | ≈ 64 g |
| Wet, post blow-down[1] – Single Layer | ≈ 70 g | ≈ 75 g |
| **Volume** | | |
| Capsule Fill Volume[2] – Single Layer | ≈ 17 mL | |
| Post blow-down Hold-Up Volume[3] – Single Layer | ≈ 11 mL | |

1 Post blow-down wet weight is defined as the experimentally measured weight of the capsule after air/gas blow-down using water as the flush fluid. Actual amount depends upon exact blow-down conditions, media type in capsule, the number of capsules in the system, the process fluid, and loading level of the capsule.

2 Capsule Fill Volume is defined as the volume of liquid required to fill the capsule (experimentally measured).

3 Post blow-down hold-up volume is defined as the estimated volume of the residual flush liquid after air/gas blow-down using water as the flush fluid, and calculated by post-blow-down weight and flush fluid density. Actual amount depends upon exact blow-down conditions, media type in capsule, the number of capsules in the system, the process fluid, and loading level of the capsule.

## F. Wetted Surface Areas

The wetted surface areas of components in 3M™ Zeta Plus™ filter cartridges and capsules are listed in Tables 8-9. For O-rings, it is estimated that 50% of the surface area is wetted. Nominal media surface areas for capsules and cartridges are listed in Table 13.

Wetted surface area calculations are based on 3D models where all geometries are represented by a finely spaced discrete set of points; curves are approximated by linear interpolation between these points. A numerical quadrature algorithm is used to estimate the surface area and volume. The listed wetted surface areas represent the nominal values with tolerances allowed in component dimensions.

| Table 8. Wetted Surface Areas of Cartridge Components | | | |
|---|---|---|---|
| **Components** | **Wetted Surface Area [cm²]** | | |
| | **8" Cartridge** | **12" Cartridge** | **16" Cartridge** |
| Separator (per lenticle) | 415 | 1373 | 4361 |
| Netting[1] (per lenticle) | - | 5970 | 12900 |
| Edge Seal (per lenticle) | 174 | 312 | 426 |
| Ring Seal (per lenticle) | 23 | 12 | 22 |
| Gasket Retainer (each) | 46 | 57 | 57 |
| Molded Lifting Handle[2] on Gasket Retainer | - | 181 | - |
| Gasket (each) | 28 | 37 | 37 |
| Film Handle[3] | - | - | 1245 |
| Binder Bands | 19 | 28 | 28 |

1 Specific 12" and 16" cartridges
2 Specific 12" cartridges
3 Specific 16" cartridges

| Table 9. Wetted Surface Areas of Laboratory Capsule Components | |
|---|---|
| **Components** | **Wetted Surface Area [cm²]** |
| | **BC0025** |
| 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 |

# V. Product Specifications and Operation Parameters

## A. Product Release Specifications

The product specifications verified during filter manufacturing and prior to the release of media lots include but are not limited to the following.

1) Specific Dry Sheet Weight – Weight of the dry filter media in g/in².
2) Pressure Drop at constant air flow – Determined by testing a 5-inch diameter disc of media sheet when challenged at a specific air flow rate.
3) Wet Tensile Strength - Determined by soaking a media coupon in water for two minutes then measuring the peak force (in kilograms) to break the sample. The result is normalized for the cross-sectional width and length.
4) Calcium Extraction - Determined by soaking media in deionized (DI) water at a ratio of 1 gram of media to 10 mL of water for 24 hours at ambient temperature and analyzing the water for soluble calcium. The result is normalized as mg of calcium per gram of media.
5) Iron Extraction - Determined by soaking media in DI water at a ratio of 1 gram of media to 10 mL of water for 24 hours at ambient temperature and analyzing the water for soluble iron. The result is normalized as mg of iron per gram of media.
6) Color Extraction - Determined by flushing a media sample with 100 mL of 0.4% w/v 180° F sodium citrate solution through a 45 mm disc sample of the media. The pooled effluent is analyzed for percent transmittance at 420 nm.
7) Organic Extraction - Determined by soaking media in DI water at a ratio of 1 gram of media to 10 mL of water for 24 hours at ambient temperature. The effluent sample is then filtered and 1 mL of filtered effluent sample is added to a cuvette with 49 mL of DI water. The final sample is analyzed for absorbance at 210 nm.
8) Endotoxin Extraction - *Limulus* Amebocyte Lysate (LAL) bacterial endotoxin reactivity - Determined by filtering sterile water through a 45 mm disc of media at a flow rate of 18-20 mL/min then collecting a 2 mL effluent sample after 49 mL. The effluent sample is tested for endotoxins using a Kinetic Turbidimetric LAL Assay.

The above specification limits for each 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP filter media grade are presented in Table 10 for US and Poland manufactured media and Table 11 for France manufactured media.

**Table 10. US and Poland Made Media Release Properties for 3M™ Zeta Plus™ CP and AP Series Filters**

| Product Release Properties | Specifications | | | | | | |
|---|---|---|---|---|---|---|---|
| | 01AP | 10CP | 30CP | 50CP | 60CP | 70CP | Units |
| Pressure Drop at Air Flow | ≤ 2.0 | 8.5 – 13.0 | 15.0 – 26.0 | 50.0 – 68.0 | 80.0 – 104.0 | 148.0 – 202.0 | Inch $H_2O$ |
| Wet Tensile Strength | ≥ 1.5 | ≥ 4.0 | ≥ 4.5 | ≥ 5.5 | ≥ 6.0 | ≥ 7.0 | Kg/in |
| Ca Extraction | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | mg/g |
| Fe Extraction | ≤ 0.010 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | mg/g |
| Color Extraction | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | Color Units |
| Organic Extraction | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | Absorbance |
| Endotoxin Extraction | ≤ 0.25 | < 0.25 | < 0.25 | < 0.25 | < 0.25 | < 0.25 | EU/mL |

**Table 11. France Made Media Release Properties for 3M™ Zeta Plus™ CP Series Filters**

| Product Release Properties | Specifications | | | | | | |
|---|---|---|---|---|---|---|---|
| | 01CP | 10CP | 30CP | 50CP | 60CP | 70CP | Units |
| Pressure Drop at Air Flow | 0.4 – 1.1 | 5.4 – 10.5 | 13.5 - 33.0 | 45.0 - 68.0 | 68.0 – 112.0 | 112.5 – 220.0 | Inch $H_2O$ |
| Wet Tensile Strength | ≥ 1.0 | ≥ 3.0 | ≥ 3.0 | ≥ 4.0 | ≥ 4.5 | ≥ 5.0 | Kg/in |
| Ca Extraction | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | mg/g |
| Fe Extraction | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | ≤ 0.040 | mg/g |
| Color Extraction | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | ≤ 8.0 | Color Units |
| Organic Extraction | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | ≤ 0.37 | Absorbance |
| 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 the 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products should follow the appropriate use instruction for each filter configuration. Always operate within the specified pressure and temperature limits.

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

Prior to filtration operation, end-users should verify that the housing for filter cartridges is integral and filter cartridges or capsules have been properly installed and sealed. Therefore, a pre-use Installation Qualification test (IQ) should be performed per recommended test procedure contained in 3M's Installation and Operating Procedures manuals (70-0201-8802-8 for cartridges, 70-0202-6945-5 for capsules).

## C. Minimum Recommended Preconditioning Flush

3M™ Zeta Plus™ depth filters made with 01AP or CP media are comprised primarily of natural products and are considered 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. Therefore, 3M recommends that customers flush the filters before exposure to their product. 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP media depth filters can be flushed with water or buffer at temperature and pressure not to exceed the maximum product specification. The minimum preconditioning flush volume for all products is 54 L/m². Pressure drop across the filter should not exceed 2.4 bar [35 psid]. The maximum recommended flux for the preconditioning flush is 1200 L/m²/hour (LMH) for cartridges. The maximum recommended flux for the preconditioning flush is 210 LMH for capsules.

If the filter is autoclaved or steam sterilized *in-situ* prior to use, 3M recommends that the product be flushed after sterilization per preconditioning flush protocols.

Detailed preconditioning flush protocols are provided in 3M Installation and Operating Instructions (see Section V.B.). Based on the minimum preconditioning flush of 54 L/m² and the nominal surface area for each filter, flush volumes for each filter configuration are provided in Table 13.

The data package of effluent quality presented in this Regulatory Support File is developed based on the maximum recommended flux of the preconditioning flush for cartridges.

| Table 12. Minimum Preconditioning Flush Volume and Recommended Flux | | |
|---|---|---|
| Minimum Preconditioning Flush Volume | All Products | 54 L/m² |
| Maximum Recommended Flux of Preconditioning Flush | Cartridges | 1200 LMH |
| | Capsules | 210 LMH |

| Table 13. Minimum Preconditioning Flush Volume & Nominal Surface Area | | |
|---|---|---|
| **Cartridge Configuration** | **Nominal Surface Area** | **Minimum Preconditioning Flush Volume [L]** |
| 45109 & Z08 (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 |
| 45116 (12" diameter cartridge, 9-cell) | 0.9 $m^2$ | 46 |
| 45115 & 45245 (12" diameter cartridge, 16-cell) | 1.5 $m^2$ | 81 |
| 45113 (12" diameter cartridge, 18-cell) | 1.8 $m^2$ | 92 |
| Z16S (16" diameter cartridge, 9-cell)[1] | 2.1 $m^2$ | 113 |
| Z16P and Z16M (16" diameter cartridge, 14-cell)[1] | 3.2 $m^2$ | 173 |
| Z16D (16" diameter cartridge, 15-cell) | 3.5 $m^2$ | 188 |
| Z16H (16" diameter cartridge, 16-cell) 30CP & 50CP only[1] | 3.7 $m^2$ | 200 |
| **Capsule Configuration** | **Nominal Surface Area** | **Minimum Preconditioning Flush Volume [L]** |
| BC0025 Laboratory Capsule | 25 $cm^2$ | 0.14 |

1 Wet weight (65 lb/ 29 kg) may require lifting assistance.

## D. Operating Conditions

| Table 14. Operating Conditions | | |
|---|---|---|
| Maximum Operating Pressure | Laboratory Capsule | 2.8 bar (40 psig) maximum inlet pressure |
| | Production Capsules | 3.4 bar @40 °C (50 psig @104 °F) |
| Maximum Differential Pressure Forward | All Products | 2.4 bar (35 psig) |
| Maximum Operating Temperature | Cartridge | 82 °C (180 °F) |
| | Capsules | 40 °C (104 °F) |
| Minimum Preconditioning Flush Volume | All Products | See Section V. C. |
| Recommended Flux of Preconditioning Flush | Cartridges | |
| | Capsules | |
| Pre-Use Sterilization | Cartridges | See Section V. E. |
| | Capsules | |

## E. Pre-Use Sterilization

3M Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products are not bioburden controlled. They can be autoclaved or *in-situ* steam sterilized per recommended conditions listed in Table 15. The filter cartridges can be steam sterilized per 3M procedure 70-0201-8840-8. Studies were conducted to ensure sterility after autoclave or *in situ* steam sterilization. If the filter is autoclaved or steam sterilized *in-situ* prior to use, 3M recommends that it be flushed after sterilization per preconditioning flush protocols.

| Table 15. Pre-Use Sterilization Conditions | |
|---|---|
| **Product Class** | **Autoclave / Steam-in-Place Parameters[1]** |
| Cartridges | *in situ* steam sterilization, 30 minutes @ 126 °C (259 °F) maximum (3 cycles Max) |
| Laboratory Capsules | Autoclave only, 30 minutes @ 121 °C (250 °F) maximum (1 cycle) |

1. Do not exceed maximum pressure and temperature ratings during sterilization.

### F. Post-Use Sanitization

3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products may be sanitized by the procedure in Table 16 prior to disposal, if necessary, to comply with local regulations or customer requirements.

| Table 16. Post-Use Sanitization Conditions[1] | | |
|---|---|---|
| **Product Class** | **Caustic Sanitization** | **Autoclave / Steam-in-Place Parameters** |
| Cartridges | Can be treated with 1M NaOH or 5% NaClO post-use. | Same as Pre-Use Sterilization Conditions (See Table 15) |
| Laboratory Capsules | Capsule soak for 1 hour with 1M NaOH or 5% NaClO (bleach)[2] post-use. | |

1. Do not exceed maximum pressure and temperature ratings during sanitization.
2. Do not use NaClO (bleach) for pre-use sanitization.

## VI. 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.

### 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 the recommended preconditioning flush.

| Table 17. Reference Industry Standards | |
|---|---|
| **USP Standards** | **Applicable Methods** |
| -- | Non-Volatile Residue |
| <643> | Total Organic Carbon |
| <645> | Conductivity |
| -- | Extractable Metals |
| <85> | Bacterial Endotoxin |
| <88> | Biological Reactivity |

## A. Total Non-Volatile Gravimetric Extractables (TNVGE)

3M™ Zeta Plus™ 10CP, 50CP and 70CP products were challenged with DI water (25°C) to a total volume of two times the minimum recommended preconditioning flush volume of 54 L/m² . Filtrate samples were collected at the 33%, 66%, 100%, 150% and 200% filter flush points of the recommended minimum preconditioning flush. These samples (of sufficient size for determination accuracy) were taken to dryness under controlled conditions until weighing vessels of constant final weights were observed.

**Table 18. Total Non-Volatile Gravimetric Extractables (TNVGE) of Zeta Plus™ CP Filter products [mg/L]**

| | 10CP | | | 70CP | | |
|---|---|---|---|---|---|---|
| **Flush Volume %** | # of Lots: 3 | | | # of Lots: 8 | | |
| [%] | Avg | Max | Min | Avg | Max | Min |
| 33% | 11.7 | 14.0 | 10.0 | 72.0 | 253 | 10.0 |
| 66% | <10 | <10 | <10 | 19.0 | 19.0 | 19.0 |
| 100% | <10 | <10 | <10 | <10 | <10 | <10 |
| 150% | <10 | <10 | <10 | <10 | <10 | <10 |
| 200% | <10 | <10 | <10 | <10 | <10 | <10 |

Flushing may reduce the Total Non-Volatile Gravimetric Extractables.

## B. USP <643> Total Organic Carbon (TOC)

3M™ Zeta Plus™ 10CP, 50CP and 70CP products were challenged with DI water (25°C) to a total volume of two times the minimum recommended preconditioning flush volume of 54 L/m² . Filtrate samples were collected at the 33%, 66%, 100%, 150% and 200% filter flush points of the recommended minimum preconditioning flush. The samples were then assayed for total organic carbon.

**Table 20. TOC of 3M™ Zeta Plus™ CP Depth Filters**

| | 10CP | | | 50CP | | | 70CP | | |
|---|---|---|---|---|---|---|---|---|---|
| **Flush Volume %** | # of Lots: 3 | | | # of Lots: 2 | | | # of Lots: 8 | | |
| [%] | Avg | Max | Min | Avg | Max | Min | Avg | Max | Min |
| 33% | 3.0 | 4.2 | 2.3 | 5.2 | 5.5 | 4.9 | 2.7 | 4.7 | 1.4 |
| 66% | 1.1 | 1.3 | 1.0 | 2.0 | 2.0 | 1.9 | 1.2 | 2.2 | 0.5 |
| 100% | 0.9 | 1.0 | 0.7 | 1.8 | 1.8 | 1.8 | 1.0 | 2.0 | 0.3 |
| 150% | 0.6 | 0.7 | 0.6 | 1.7 | 1.7 | 1.7 | 0.8 | 1.9 | 0.3 |
| 200% | 0.5 | 0.6 | 0.4 | 1.5 | 1.6 | 1.5 | 0.7 | 1.9 | 0.2 |

Flushing may reduce the Total Organic Carbon of the effluent.

## C. USP <645> Conductivity

3M™ Zeta Plus™ 10CP, 50CP and 70CP products were challenged with DI water (25°C) to a total volume of two times the minimum recommended preconditioning flush volume of 54 L/m² . Filtrate samples were collected at the 33%, 66%, 100%, 150% and 200% filter flush points of the recommended minimum preconditioning flush. The samples were then assayed for conductivity.

**Table 21. Conductivity of 3M™ Zeta Plus™ CP Depth Filters [µS/cm]**

| | 10CP | | | 50CP | | | 70CP | | |
|---|---|---|---|---|---|---|---|---|---|
| **Flush Volume %** | # of Lots: 3 | | | # of Lots: 2 | | | # of Lots: 8 | | |
| [%] | Avg | Max | Min | Avg | Max | Min | Avg | Max | Min |
| 33% | 21.2 | 22.5 | 20.6 | 165.4 | 177.7 | 153.2 | 89.5 | 223.9 | 32.8 |
| 66% | 7.2 | 7.8 | 6.6 | 30.0 | 35.2 | 24.8 | 28.7 | 44.7 | 12.7 |
| 100% | 4.9 | 5.3 | 4.3 | 18.7 | 24.5 | 12.8 | 21.8 | 36.3 | 7.7 |
| 150% | 3.4 | 3.6 | 3.1 | 15.0 | 20.0 | 9.9 | 16.1 | 27.6 | 5.1 |
| 200% | 2.5 | 2.7 | 2.4 | 12.0 | 16.2 | 7.8 | 11.4 | 25.3 | 3.3 |

Flushing may reduce the conductivity of the effluent.

D. Extractable Metals (Al, As, Ca, Fe, K, Mg, Na, Pb, Si)

3M™ Zeta Plus™ 10CP, 50CP and 70CP products were challenged with DI water (25°C) to a total volume of two times the minimum recommended preconditioning flush volume of 54 L/m² . Filtrate samples were collected at the 33%, 66%, 100%, 150% and 200% filter flush points of the recommended minimum preconditioning flush. Levels of soluble metal extracts in these samples were determined using Inductively Coupled Plasma Atomic Emission Spectrometry (ICP-AES).

**Table 19. Metals Analysis of Extraction Solutions [ppb] of 3M™ Zeta Plus™ CP Depth Filters**

| Flush Volume % | | | Metals Concentration [ppb] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Al | As | Ca | Fe | K | Mg | Mn | Na | Pb | Si |
| 10CP | Max of 3 lots | 33% | 33% | 490 | <50 | 730 | 86 | 1400 | 310 | 35 | 5100 | ND |
| | | 66% | 66% | 160 | <50 | 370 | 39 | 760 | 100 | 12 | 1900 | ND |
| | | 100% | 100% | 86 | <50 | 130 | 24 | 460 | 45 | 6 | 1100 | ND |
| | | 150% | 150% | 40 | <50 | 57 | 10 | 260 | 20 | <5 | 4200 | ND |
| | | 200% | 200% | 21 | <50 | 32 | 5.4 | 160 | 11 | <5 | 470 | ND |
| 50CP | Max of 2 lots | 10% | 10% | 2463 | <1 | 4592 | 94 | 5580 | 1724 | 91 | 69603 | ND |
| | | 100% | 100% | <120 | <1 | ND | 4.5 | 186 | 35 | ND | 493 | ND |
| | | 200% | 200% | <120 | <1 | ND | 5 | 126 | 22 | ND | 285 | ND |
| 70CP | Max of 8 lots | 33% | 73 | <50 | 380 | 23 | 310 | 150 | <5 | 3000 | ND | 59 |
| | | 66% | 16 | <50 | 120 | <5 | 130 | 45 | <5 | 810 | ND | <50 |
| | | 100% | 11 | <50 | 65 | <5 | 100 | 26 | ND | 520 | ND | <50 |
| | | 150% | <10 | <50 | 50 | 29 | <100 | 15 | ND | 390 | ND | <50 |
| | | 200% | <10 | <50 | 27 | <5 | <100 | 11 | ND | 290 | ND | <50 |

E. USP <85> Bacterial Endotoxin

The release of 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter media includes the determination of filtrate bacterial endotoxins for each lot. Filter discs are challenged with Sterile Water for Infection (SWFI) at 25°C, in accordance to 3M's minimum recommended preconditioning flush of 5 L/ft² (54 L/m²) of effective area. The specification limit for bacterial endotoxins is <0.25 EU/mL for 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series media manufactured in the US and Poland and ≤0.25 EU/mL for 3M™ Zeta Plus™ CP Series media manufactured in France.

Note the release specification is based on a dynamic flush protocol that does not necessarily reflect the total endotoxin amount in the media. Therefore, the extractable endotoxin amount may be impacted if using a different challenge fluid under different test conditions (*i.e.*, pH, conductivity, protein, *etc*.).

Cellulose is a raw material used in 3M™ Zeta Plus™ media. Cellulose may contain β-Glucan, which is a non-endotoxin LAL-reactive material. However, the presence of β-Glucan in any 3M™ Zeta Plus™ media flush effluent may cause an interference or enhancement of endotoxin measurement. Thus, a β-Glucan blocking buffer or LAL reagent may be used to minimize interference in the product release test. USP <85> "Bacterial Endotoxins Tests" supports these strategies during extractable endotoxin measurement in the presence of β-Glucan.

## VII. Shelf Life

**Shelf Life of 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series Converted Media Sheets, Cartridges, and Capsules:**

3 years at a recommended storage temperature of 5ºC - 30ºC, stored in original package

## VIII. Regulatory Compliance

### A. USP <88> Class VI - 70°C$_{minimum}$ Biological Reactivity Tests, *In Vivo*

Representative media grade samples and wetted components or wetted component materials of 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP products were tested and met the requirements of USP <88> Class VI, Biological Reactivity Tests, *In Vivo* at either 121°C or 70°C extraction temperature.

### B. BSE/TSE (animal derived materials)

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 resins used in the molded parts and over-molds 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.

### C. FDA CFR Title 21

While 3M has evaluated 3M™ Zeta Plus™ CP media per the standards codified in the US Food and Drug Administration's (FDA) Code of Federal Regulations (CFR), Title 21 Parts 177.2260 Indirect Food Additive – Filters, resin-bonded, as described below, 3M does not intend the product for use in any food contact application. This information is being provided only to aid customer's evaluations, risk assessments and regulatory submissions specifically for uses and applications that are consistent with 3M's Intended Use statement. See also 3M's Restricted Use statement for this product.

The media present in 3M™ Zeta Plus™ CP series filter products meets US FDA 21 CFR Part 177.2260 Indirect Food Additive – Filters, resin-bonded Sections G, H and J. For details related to specific use conditions or limitations please contact your 3M Representative for more information.

Customer and user remain responsible for determining whether a 3M product is suitable and appropriate for their specific application, and for complying with all regulations applicable to their product in the countries where it will be produced, distributed or used, including any required registrations and/or certifications with governing regulatory authorities.

## IX. Quality Assurance

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

Certificates are provided in support of the release of the 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products.

The 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP 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.

The 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products are not regulated under the OSHA Hazard Communication Standard (CFR Title 29 1910.1200). A Safety Data Sheet (SDS) is not required for these products.

Article Information Sheets for 3M™ Zeta Plus™ 01AP and 3M™ Zeta Plus™ CP Series filter products are available in the US as courtesy.

**Intended Use(s):** 3M™ Zeta Plus™ single-use filter products are intended for use in biopharmaceutical processing applications of aqueous and chemical based pharmaceuticals (drugs) and vaccines in accordance with the product instructions and specifications, and cGMP requirements, where applicable.

Since there are many factors that can affect a product's use, the customer and user remain responsible for determining whether the 3M product is suitable and appropriate for the user's specific application, including user conducting an appropriate risk assessment and evaluating the 3M product in user's application.

**Restrictions on Use:** 3M advises against the use of these 3M products in any application other than the stated intended use(s), since other applications have not been evaluated by 3M and may result in an unsafe or unintended condition. Do not use in any manner whereby the 3M product, or any leachable from the 3M product, may become part of or remains 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 Regulation (MDR), c) Japan Pharmaceuticals and Medical Devices Agency (PMDA) or in applications involving permanent implantation into the body; Life-sustaining medical applications; Applications requiring food contact compliance.

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