ZETA PLUS® VR SERIES

Viral Reduction Depth Filters

VR Series For Enhanced Log Reduction of Viruses From Biological Fluids

Application

The removal and/or inactivation of contaminating viruses from biotherapeutics is a requisite for ensuring final product safety. Zeta Plus® VR cartridge depth filters remove significant levels of viruses from biological fluids. They provide validatable viral titer reduction, high flow rates, scalability, economy, disposability and ease-of-use in the biological manufacturing environment. The VR Series includes specific filter media recommendations for virus removal from blood plasma proteins and bioprocess derived cell culture fluids.

Virus Removal Applications for Zeta Plus® VR Media :

- Processing of human plasma-derived proteins
- Recombinant proteins from cell culture and fermentation
- Monoclonal antibodies
- Serum and other raw materials derived from animal sources

Zeta Plus® depth filtration offers an attractive and economical alternative to other available technologies for reduction of viral burden. Zeta Plus® VR Series depth filters can be used as a bolt-on processing step to existing in-process viral clearance methodologies, providing an added measure of end-product safety.

Features	Benefits
Combined adsorption & physical entrapment virus removal mechanisms	Validatable viral log reduction
	Provides added level of viral safety
Quality Control tested for media adsorption capacity	Assurance of filter media consistency & performance
	Single-use, disposable design eliminates validation concerns associated with reusable clearance options (chromatography column sanitization & regeneration)
Self-contained, single-use disposable capsules & cartridge modules	Eliminates concern over virus carryover from one purification cycle to the next
Range of cartridge sizes, sanitary design cartridge housings & disposable capsules	Facilitates scaleup from small volume feasibility trials & validation studies to production scale operations
	Enable high flow processes
Optimised cartridge designs for biologicals filtration	Robust in-situ steam-sterilisable cartridges
	Drug Master Files simplify FDA submissions
Complete technical, regulatory & validation support	Regulatory Support Files detail filter media regulatory compliance & safety data
	Provides added level of validatable viral clearance
Economical “bolt-on” separation technology as adjunct or prefilter to other viral clearance steps	Can replace or augment chromatography columns or function as prefilter to final virus removal membrane filter

Regulators (FDA) recommend validation clearance via a combination of removal (filtration, chromatography) and inactivation (temperature, pH, solvent) steps where multiple methods of virus clearance are required to assure product safety.

Zeta Plus® VR Filter Selection

A range of cartridge sizes is available for varying batch size, so scale-up is easy and predictable from lab-scale, to pilot plant, to full production scale. Three different cartridge sizes (8, 12 and 16" diameter) make scale-up straightforward and predictable. Zeta Plus® cartridges are used in a flow-through mode, enabling the process stream to be passed through the filter cartridge while viruses are retained within the depth filter matrix. Small, low area disposable BioCap® capsules are available for laboratory scale and process development work and are ideal for scaled down viral validation studies.

Zeta Plus® Filter Mechanisms of Virus Removal

Zeta Plus® filter media is a family of cellulosic depth filtration media designed to retain contaminants by both physical entrapment and adsorption. It is composed of high-area process filter aids embedded in a cellulose fibre depth matrix. During the manufacturing process, a cationic charge modifier is chemically bound to the matrix components, forming a permanent, interconnected, rigid depth filter with positively-charged electrokinetic capture sites. The resulting porous depth filter structure is a tortuous network of adsorptive flow channels capable of retaining contaminating viruses through a combination of adsorption and mechanical entrapment. Cumulative viral titer reduction may also be attainable through a staged two-step Zeta Plus® system.

Zeta Plus® depth filtration is a key component in biopharmaceutical production schemes for clarifying cell culture fluids (cell separation) and is utilized worldwide in the fractionation of human and animal plasma proteins.

Selection Guide - Zeta Plus® VR Filter Media

A range of Zeta Plus® VR depth filter media is available for viral reduction from plasma proteins and bioprocess-derived (cell culture) proteins. Specific recommendations for each application are provided in Table 1 below. VR filter media is available in a range of porosities. Each VR filter media is tested and optimised for biologicals and bioprocess filtration (pharmaceutical-grade).
All cartridge and capsule components have been USP Class Vl tested for biological safety.

Table 1

Selection of Zeta Plus® VR Series Filter Media

	Recommended for:					
Filter Media Choice	**Plasma Proteins**	**Cell Culture Proteins**	**Nominal Retention Rating (µm)**	**20°C Water Flow @ 345 mb (Lpm/m²)**	**Autoclavable or In-situ Steam Sterilisable**	**[Al³⁺] in 20°C water @ 54 l/m²**
VR 01	♦		0.8	50	No	40
VR 02	♦	♦	0.8	77	Yes	20
VR 03		♦	0.8	50	Yes	40
VR 04	♦		0.45	37	No	20
VR 05		♦	0.2	16	Yes	40
VR 06	♦	♦	0.2	24	Yes	20
VR 07	♦	♦	0.2	16	Yes	60

Viral Reduction Validation

Many factors influence the choice of process steps to be studied when performing viral clearance evaluation and validation. Viral clearance validation studies are performed with a select panel of model viruses. Different virus panels are chosen to validate blood and plasma products, and separately, cell-culture derived products.

Virus removal efficiency may *be dependent on fluid and processing conditions and is best determined during qualification and validation studies using suitable virus model systems in a controlled laboratory study*. Contact CUNO Scientific Applications Support Services (SASS) for further technical advice concerning validation of viral reduction with Zeta Plus® VR depth filters.

Data is available which confirms the ability of Zeta Plus® VR depth filter media to function as an effective and validatable viral log reduction filter. Table 2 illustrates results for a reported viral clearance study utilising Zeta Plus® VR depth filters.

Table 2

Viral Clearance In An Immunoglobulin Production Process

Cumulative Virus Titer Reduction (Log_{10})					
Process Step	**BVD**	**EMC**	**HIV**	**PPV**	**PRV**
Solvent detergent	> 4.3	—	> 5.3	—	> 7.3
Supernatant III	1.4	4.3	6.1	4.7	3.8
Zeta Plus® VR 03 Depth Filtration	4.8	4.5	4.7	3.7	5.4
Total Cumulative Reduction	> 10.5	8.8	> 16.1	8.4	> 16.6

Source : D. Revie, *Novel Validation Approaches to Obtain Maximum Viral Clearance from an Immunoglobulin Production Process, IBC 2nd International Symposium on Viral Clearance, Philadelphia, PA, June, 1998.*

Quality Control of Zeta Plus® VR Series Filters

CUNO applies rigorous Quality Control testing and standards both during in-process manufacturing and during final lot release. This testing ensures consistent filter media performance in critical virus removal applications. A Certificate of Quality is provided with each VR Series filter cartridge and disposable BioCap® capsule.

Each grade of Zeta Plus® VR Series filter media is Quality Control tested on a lot release basis for the presence and magnitude of positive charge.
Summarized in Table 3 are key quality control test parameters and lot release test criteria applied to VR Series filters.

Table 3

Quality Control of Zeta Plus® VR Series Filters

Filter media (µm)	* Test for Filter Media Charge Capacity	* Optimized & Tested for Low Al Extractables	* Filter Materials Optimized for Low LAL-RM	Non-pyrogenic per USP Endotoxin Test	100% 21 CFR Listed Materials	Supplied with Certificate of Quality	USP Class VI Biological Tests
VR 01 (0.8)	Yes	No	No	Yes	Yes	Yes	Pass
VR 02 (0.8)	Yes	Yes	Yes	Yes	Yes	Yes	Pass
VR 03 (0.8)	Yes	No	No	Yes	Yes	Yes	Pass
VR 04 (0.45)	Yes	Yes	No	Yes	Yes	Yes	Pass
VR 05 (0.2)	Yes	No	No	Yes	Yes	Yes	Pass
VR 06 (0.2)	Yes	Yes	Yes	Yes	Yes	Yes	Pass
VR 07 (0.2)	Yes	Yes	No	Yes	Yes	Yes	Pass

** Indicates filter media manufacturing lot is sampled and tested as lot release test criteria*

Zeta Plus® VR Disposable Capsules, Filter Cartridges, and Filter Sheets - Configured to Suit Your Every Need

Zeta Plus® VR Series filter products are highly scaleable and can be used for applications ranging from millilitre lab volumes to production scale operations. Filter media is available in the following configurations:

VR Filter Sheets

VR filter media is available in a range of filter sheet sizes to fit plate-and-frame filter presses (contact CUNO for specific sheet sizes and part numbers).

BioCap® Disposable VR Filter Capsules

VR filter media is available in three different sizes of BioCap® disposable capsules for bench scale and pilot scale filtration (filter areas of 25 cm², 650 cm², and 1300 cm²). For more information on BioCap® disposable assemblies, including operating specifications.

VR Filter Cartridges and Sanitary Housings

VR filter media is available in 8”, 12” and 16” diameter, easy-to-use, disposable cartridges, providing surface areas from 650 cm² to 3.2 m² per cartridge. A range of sanitary design Zeta Plus® filter housings is available for VR Series cartridges.

Zeta Plus® VR Series filter media is available in a wide range of cartridge sizes including 8”, 12”, and 16” diameter filter cartridges for varying flow rates and batch volumes. CUNO’s sanitary design ZPC and ZPB Zeta Plus® filter housings are designed for pharmaceutical and biological manufacturing environments. For more information on Zeta Plus® sanitary filter housings, contact CUNO.

SCIENTIFIC APPLICATIONS SUPPORT SERVICES (SASS)

CUNO’s 90+ years of experience are synonymous with quality, performance and high level technical support. The cornerstone of CUNO’s philosophy is service to customers, not only in product quality and prompt delivery, but also in validation, in applications support and in the sharing of scientific information. CUNO’s Scientific Applications Support Services group works closely with customers to solve difficult separation problems and to recommend the most economical and efficient filter systems. SASS specialists routinely work with third-party contract laboratories to validate Zeta Plus® filters for viral clearance applications. Contact CUNO’s SASS group for more details on viral validation support.

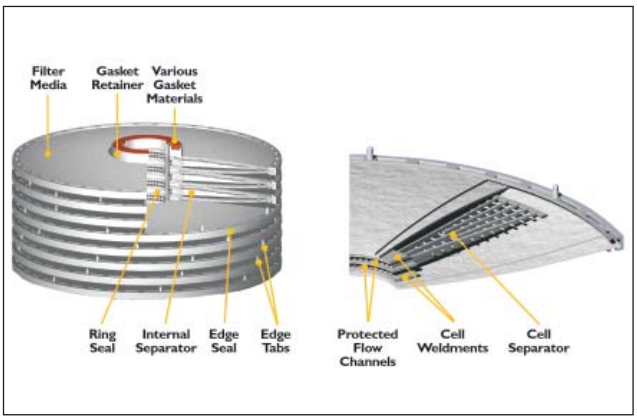
RECOMMENDED OPERATING PARAMETERS

Nominal Retention Ratings	0.2 to 0.8 micron
Maximum Operating Pressure	*VR Cartridges :* 2.4 bar maximum cartridge pressure drop. *BioCap® 25 Capsules :* 2.75 bar maximum inlet pressure, 2.4 bar maximum media pressure drop. *BioCap® 1000 / 2000 Series Capsules :* 5.5 bar at 25°C, 4.1 bar at 60°C, maximum inlet pressure ; 2.4 bar maximum cartridge pressure drop.
Maximum Operating Temperature	*Zeta Plus® VR 02, 03, 05, 06 & 07 Cartridges* : 82°C. *Zeta Plus® VR 01 & 04 Cartridges* : 60°C. *BioCap® 25 Capsules* : 40°C. *BioCap® 1000 / 2000 Capsules* : 60°C.
Recommended Pre-use Rinse	54 l/m² @ 20 lpm/m²
Sterilization Parameters	All media grades can be autoclaved or in-situ steam sterilized, except VR 01 & VR 04 (refer to Table 1.) *Zeta Plus® VR Cartridges* : In-situ steam sterilized or autoclaved for 30 minutes at 121° C, 1 cycle. *BioCap® 25* : Autoclave for 30 minutes at 121° C (1 cycle). *BioCap® 1000 / 2000* : Autoclave for 30 minutes at 121° C (up to 3 cycles).
Operating FLUX range	1.2 - 12 lpm/m²

SURFACE AREA FOR ZETA PLUS® VR FILTER PRODUCTS :

Nominal Surface Area	
BioCap® 25 Capsule	25 cm²
BioCap® 1000 Capsule	650 cm²
BioCap® 2000 Capsule	1300 cm²
45109 (8" diameter cartridge, 8-cell)	2600 cm²
45167 (8" diameter cartridge, 7-cell, O-ring, plug-in)	2300 cm²
Z8FA2NPX2 (8" diameter cartridge, 2-cell plug-in)	650 cm²
Z8FA4NPX2 (8" diameter cartridge, 4-cell plug-in)	1300 cm²
45264 (12" diameter cartridge, 7-cell bodyfeed)	0,67 m²
45245 (12" diameter cartridge, 16-cell)	1.5 m²
Z16P (16", 14-cell, netted)	3.20 m²

CARTRIDGE CONSTRUCTION :



VR SERIES ORDERING GUIDE - DISPOSABLE CARTRIDGE AND CAPSULE PRODUCTS

8" DIAMETER CARTRIDGES

CATALOGUE NUMBER	GASKET	PKG. CODE	VR SERIES
45109 (8", 8-Cell)	**11** - Nitrile **13** - Fluorocarbon **14** - EPR **22** - Silicone		**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**
45167 (8", 7-Cell, O-ring Plug-in)	**01** - Nitrile **02** - EPR **03** - Fluorocarbon **04** - Silicone		**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**
Z8FA2NP (8", 2-Cell, Plug-in) **Z8FA4NP** (8", 4-Cell Plug-in)	**A** - Silicone **B** - Fluorocarbon **C** - EPR **D** - Nitrile	**2**	**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**

16" DIAMETER CARTRIDGES

CATALOGUE NUMBER	GASKET	VR SERIES
Z16P (16", 14-Cell)	**A** - Silicone **B** - Fluorocarbon **C** - EPR **D** - Nitrile	**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**

BIOCAP® CAPSULES

CATALOGUE NUMBER	VR SERIES
BC 0025L (Luer) - 25 cm² area **BC 0025S** (Sanitary) - 25 cm² area **BC 1000A** (single pack) - 650 cm² area **BC 1000B** (3 pack) - 650 cm² area **BC 2000A** (single pack) - 1300 cm² area **BC 2000B** (3 pack) - 1300 cm² area	**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**

12" DIAMETER CARTRIDGES

CATALOGUE NUMBER	GEOMETRIC VARIATION	GASKET	VR SERIES
45264 (12", 7-Cell Bodyfeed) **45245** (12", 16-Cell)	**01** - Standard Polypropylene	**A** - Silicone **B** - Fluorocarbon **C** - EPR **D** - Nitrile	**VR 01 VR 05** **VR 02 VR 06** **VR 03 VR 07** **VR 04**

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