3M Solutions for Biopharmaceutical Process Development, Manufacturing and Process Monitoring

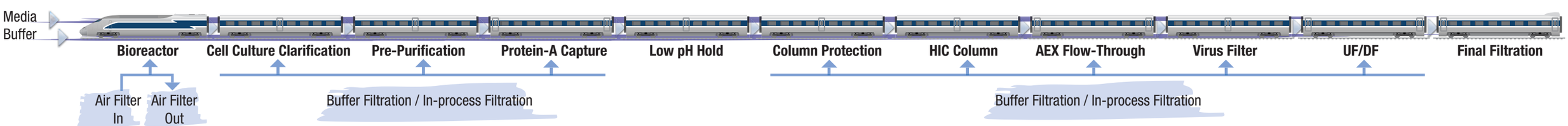
3M Is The Innovation Company That Makes Progress Possible

- We create transformational products and solutions that enable customer success and improve people's lives around the world.
- We utilize a collaborative, high-energy approach to solve the toughest problems across industries and markets by:
  - Constantly exchanging and building on each other's ideas
  - Uncovering new connections between seemingly unrelated markets and more than 50 diverse technology platforms
  - Fostering a culture of intellectual curiosity and creativity that pushes boundaries

At 3M, we are advancing the global biopharmaceutical industry by helping to build better and more efficient manufacturing processes, improving product safety by providing tools for monitoring and tracking, and reducing energy usage with our technologies. The Life Sciences Process Technologies business unit of 3M Purification Inc. provides cutting edge technologies to address clarification, filtration and purification needs of the global biopharmaceutical industry.

3M Technologies for Biopharmaceutical Applications

Figure 1: The Biopharmaceutical Production and Downstream Purification Train



3M Technology, Products and Innovation

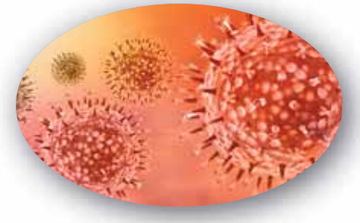
Advancing the Biopharma Industry

3M Technologies

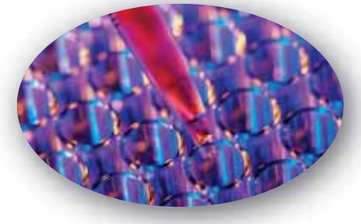
At 3M, our technology, products and innovation reflect what we do for our customers every day: advance, enhance and improve their products and processes to enable their success.

3M Purification's dedicated technical services and laboratory personnel help solve customer's most arduous separations problems. Our engineers work to provide solutions that reduce the overall cost of ownership. Our researchers are constantly working on breakthroughs that make new separations platforms possible.

Every day our products are used by researchers, process developers and manufacturing personnel for critical filtration, separation and process monitoring steps in the biopharmaceutical industry.



Viral Based Therapeutics



Diagnostics Reagents & Serum Filtration

Bacterial and Yeast Based Cell Culture, e.g. Insulin

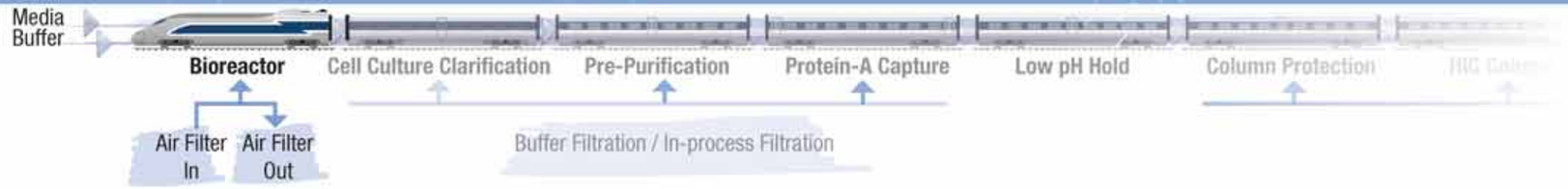
Follow-on Biologics — Biosimilars & Bio-betters

Mammalian Cell Culture — e.g. Monoclonal Antibodies, Fusion Proteins

Biopharmaceutical Separations Applications

Biopharmaceutical refers to biologically active therapeutic and diagnostic proteins that are expressed by mammalian, insect, yeast or bacterial cells. Such drugs can be classified into: monoclonal antibodies, growth factors, hormones, cytokines, fusion proteins, and therapeutic enzymes. Viral based therapeutics are poised to grow rapidly and hold great promises for disease treatment in the future. The manufacturing process of diagnostic reagents and sera contains many biopharmaceutical separations applications.

Filtration and purification plays an essential role in manufacturing of biopharmaceutical drugs. 3M offers a range of filtration, purification and process monitoring technologies that can be used in both upstream and downstream steps in every scale of biopharmaceutical manufacturing.



3M Products for Use with Bioreactors

The Bioreactor is at the heart of a biopharmaceutical manufacturing process. For the bioreactor to work at maximal efficiency, filters used for air and media filtration need to completely remove foreign microorganisms.

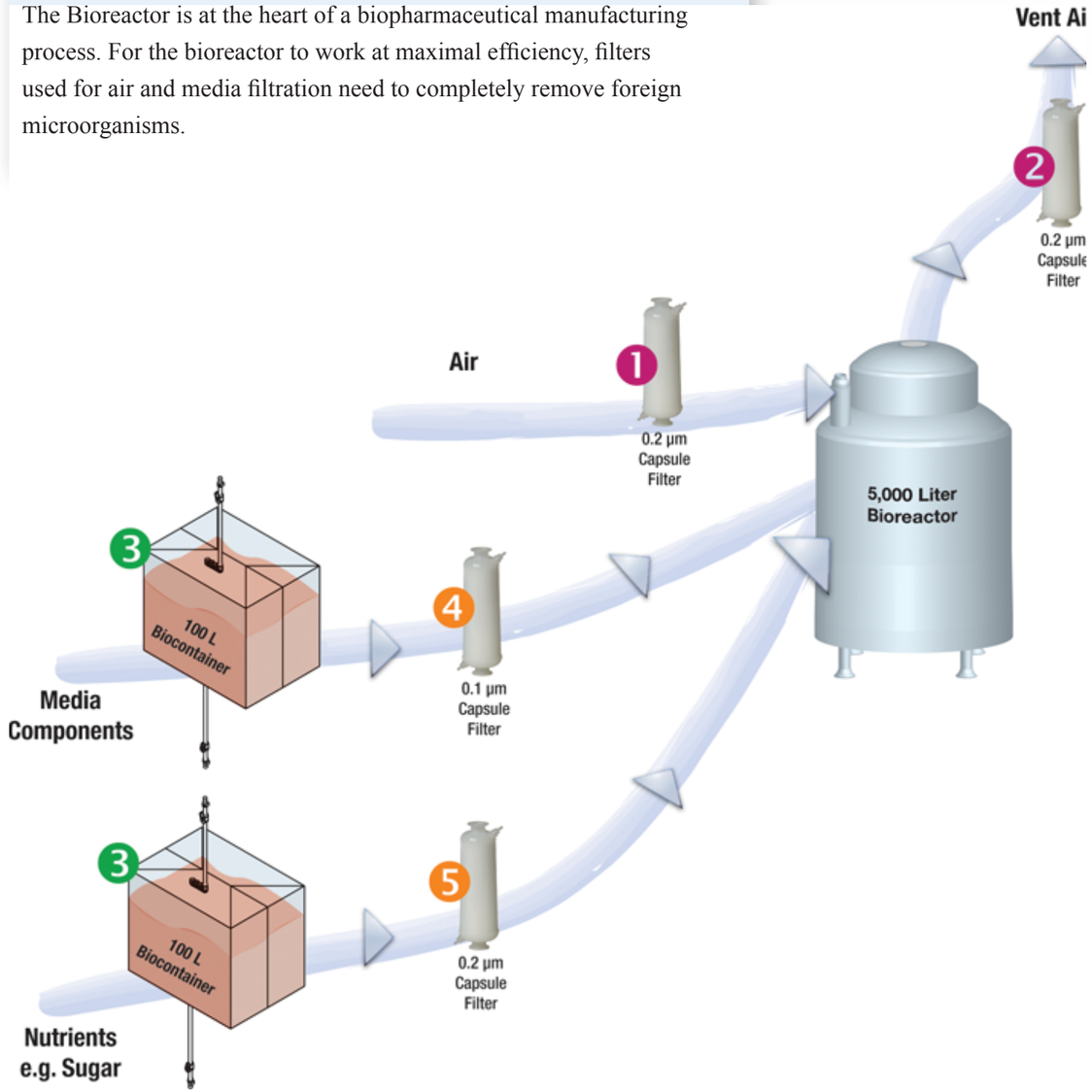


Figure 2: 3M Purification Filters and Biocotaniers for use with Bioreactors

	1 Air Filtration	2 Vent Air Filtration	3 In Process Storage	4 Filtration Of Media Components	5 Filtration Of Nutrients/Buffers	Automated Integrity Tester For Housings And Connections	Surface Cleanliness Monitoring
Scope of application†	Retention of bacteria and aerosolized bacteriophage		Short term storage of media, buffers etc.	High LRV removal of mycoplasma for media components	Reliable removal of bacteria from nutrients / buffers	Portable handheld integrity tester to measure pressure decay.	Real-time monitoring of microbial / protein residues from surfaces
Filter Pore Size	0.2 µm		Not Applicable	0.1 µm	0.2 µm	Not Applicable	Not Applicable
3M Products	LifeASSURE™ PFS 		3M™ Single-Use Biocontainer 	LifeASSURE™ PSA 	LifeASSURE™ PDA 	MiniCheck™ 	3M CleanTrace™ 
Materials	PTFE membrane Filter		Proprietary Multi-layer Film (LDPE contact layer)	Nylon membrane Filter	PES membrane Filter (Sterile and *Gamma* Compatible)	Electronic Instrument	Electronic Instrument with consumables
Validation of operating properties	Validated for sterilizing performance using a liquid bacteria *B. diminuta* (ATCC 19146) at challenge levels of a minimum of 10^7 CFU/cm² for reliable sterilizing performance in wet or dry conditions Complete bacteriophage retention using aerosol challenge test methods		Detailed validation package outlining extractables including LC/GC-MS data with various buffers and chemicals	Absolute retention of *Acholeplasma laidlawii*, ATCC 23206 at challenge levels of > a minimum of 10^7 CFU/cm²	Absolute retention of *B. diminuta* (ATCC 19146) at challenge levels of > a minimum of 10^7 CFU/cm²	Microprocessor driven, programmable system (with available printer) for determining leak integrity of closed pressurized systems (e.g. Filter and housings)	3M Clean-Trace™ Surface and Water ATP tests help assess standards of hygiene and cleaning procedures by measuring the amount ATP or proteins

Bacterial Fermentation e.g. *Escherichia coli*†

Developed in the late 1970s, the bacterial expression system, such as the *E. coli* system, is used to produce many important therapeutic recombinant proteins. The popularity and dominance of the bacterial system has continued until today because of its advantage in speed, simplicity and cost. The challenge of using this system is in downstream purification. A homogenization step after harvest is often needed because most of the expressed proteins are located in inclusion bodies rather than secreted outside the cells. This step increases the level of lipids, host cell proteins, DNA and endotoxins along with the target protein; hence resulting solutions from bacterial harvest are difficult to purify.

Mammalian Fermentation e.g. CHO Cell†

Mammalian cells (e.g., CHO [Chinese Hamster Ovary] Cells) are typically used to produce monoclonal antibodies. Monoclonal antibodies are derived from one single clone and thus are identical in structure. Today over 30 monoclonal antibodies have been approved in the U.S. with indications for a variety of difficult to treat diseases such as autoimmune diseases, cancers, infectious diseases, etc. Clarification involves separation of the cells from bulk media. Cell density (> typical 5 x 10^6 cells/mL) and cell viability affect the depth filtration step. In general, mammalian cell cultures are easier to filter than bacterial cell culture harvests.

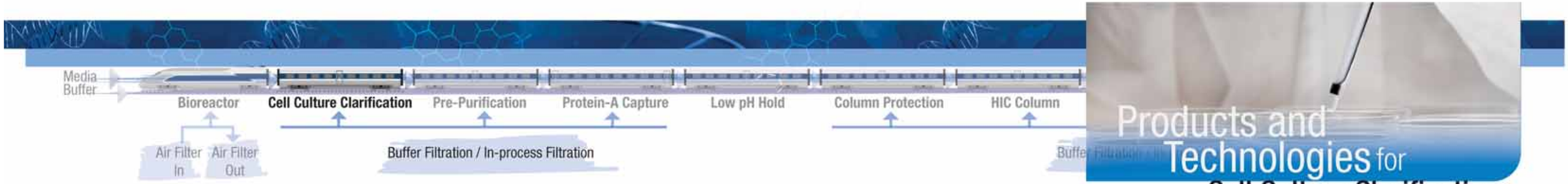
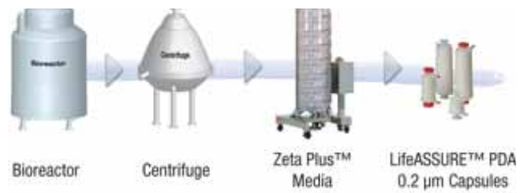


Figure 3: Cell Clarification Set-Up†

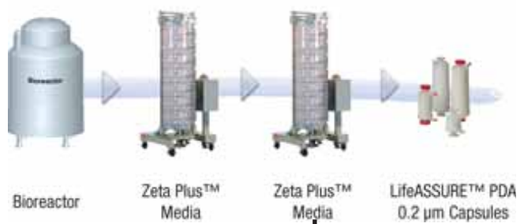
3M offers the most comprehensive portfolio of depth filters for cell culture clarification in the biopharmaceutical industry. Zeta Plus™ depth filtration technology, in cartridge systems and sheets, play an important role in the clarification of cell-derived protein therapeutic products around the world. 3M is recognized as a market leader in depth filter technology.

Centrifuge Method



Bacterial Cell Culture	Zeta Plus 60ZA05A or 90ZA08A Media
Mammalian Cell Culture	Zeta Plus 60ZA05A Media

Depth Filtration Method



Bacterial Cell Culture	Zeta Plus 60SP02A Media
Mammalian Cell Culture	Zeta Plus 60SP02A or 90ZA08A Media

Table 1: Depth Filter Media Recommendations†

Feed Composition	Fluid Turbidity	Recommendation
Whole cells, hard particles (density gradient). First clarification.	> 300 NTU	• Centrifuge • TFF • Open pore depth filter (05 or 10 SP)
Colloidal, Cell Debris	100-300 NTU	• Medium Pore Depth filter 30-60 SP
Colloidal, Small Particulates	20-100 NTU	• 60SP or 60ZA or 90 ZA
Fine particulates, colloidal (Final Polishing)	< 10 NTU	• 90 or 120 ZA
Intra-cellular, requires cell breakage – First Clarification Step	> 300 NTU	• Centrifuge

Figure 4: Zeta Plus™ Depth Filter Family

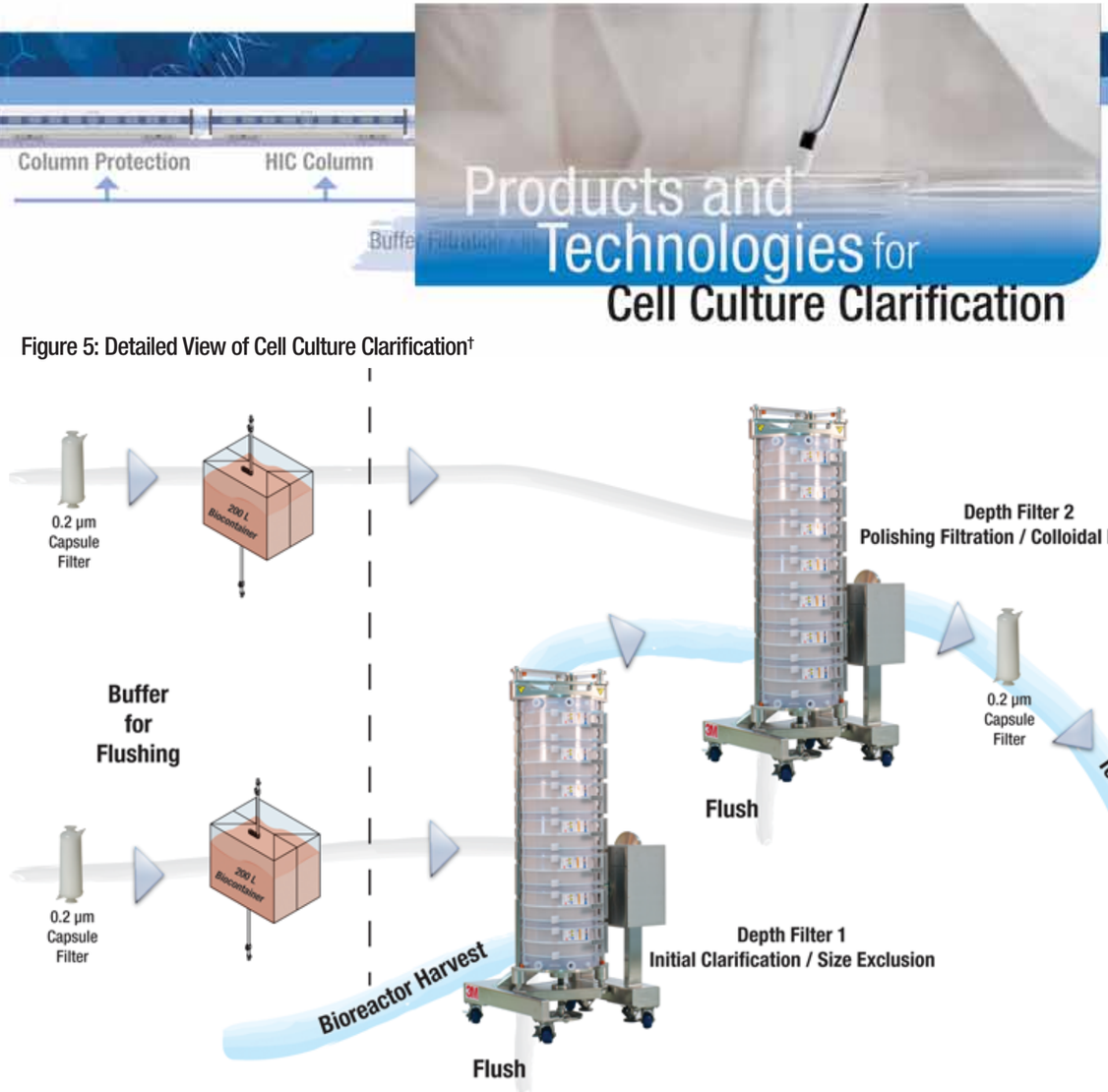


Figure 5: Detailed View of Cell Culture Clarification†

Table 2: Range of Media Adsorption Properties

Designation	Media Surface Characteristic
ZA	Strong Anion-Exchange
SP	Medium Anion-Exchange
HP	Weak Anion-Exchange High Wet Strength
ZC	Activated Carbon for color / organic adsorption
DELI	Activated Silica for adsorption of hydrophobic moieties

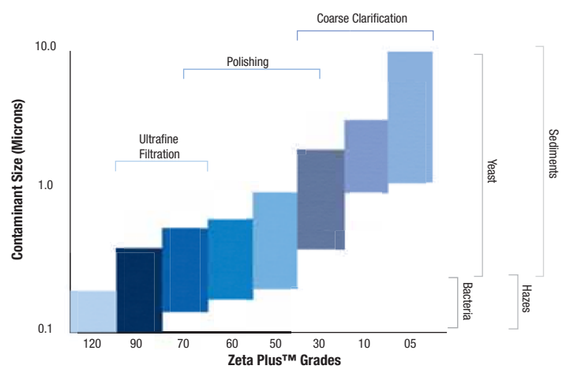
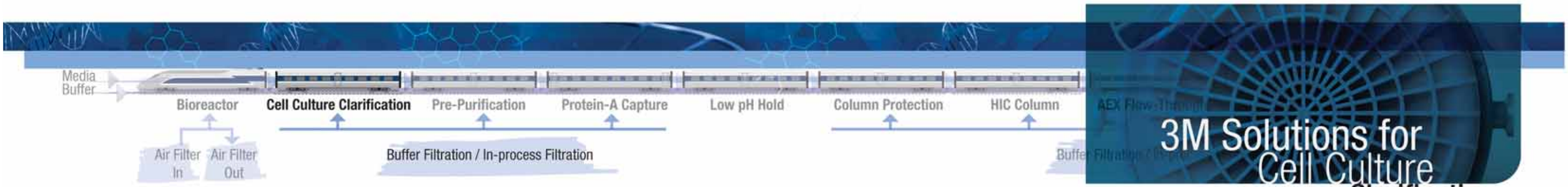


Figure 6: Wide Choice of Media Grades

Products and Technologies for Cell Culture Clarification



3M Solutions for Cell Culture Clarification

Traditional Solutions for Cell Culture Clarification

Based on our more than 30 years of technical expertise in filtration and separation products for the biopharmaceutical industry, we offer:

1. The broadest portfolio of lenticular depth filter media in the industry
2. Complex custom engineered systems
3. Single-use storage solutions and customized connector sets
4. Tools for integrity testing of filter systems, handheld pressure decay measurement systems
5. Range of sterile and *gamma* compatible 0.2 µm PES membrane capsules

Zeta Plus™ 1
Lenticular Cartridges

2
Complex Custom
Engineered Solutions

3
3M™ Single-Use
Biocontainers

4
Tools for
Integrity Testing of
Filtering System

5
LifeASSURE™ PDA
0.2 µm Sterile Capsules

Single-Use Solutions for Cell Culture Clarification

3M offers a complete package of single-use systems for cell culture clarification applications for biopharmaceutical customers. Single-use Zeta Plus™ Encapsulated depth filter clarification solutions are available in scaleable capsule formats from R&D to process development to pilot / clinical production to commercial and large scale production. In addition, we also offer customized solutions and accessories, such as tubing connectors and staging carts to round out a complete package.

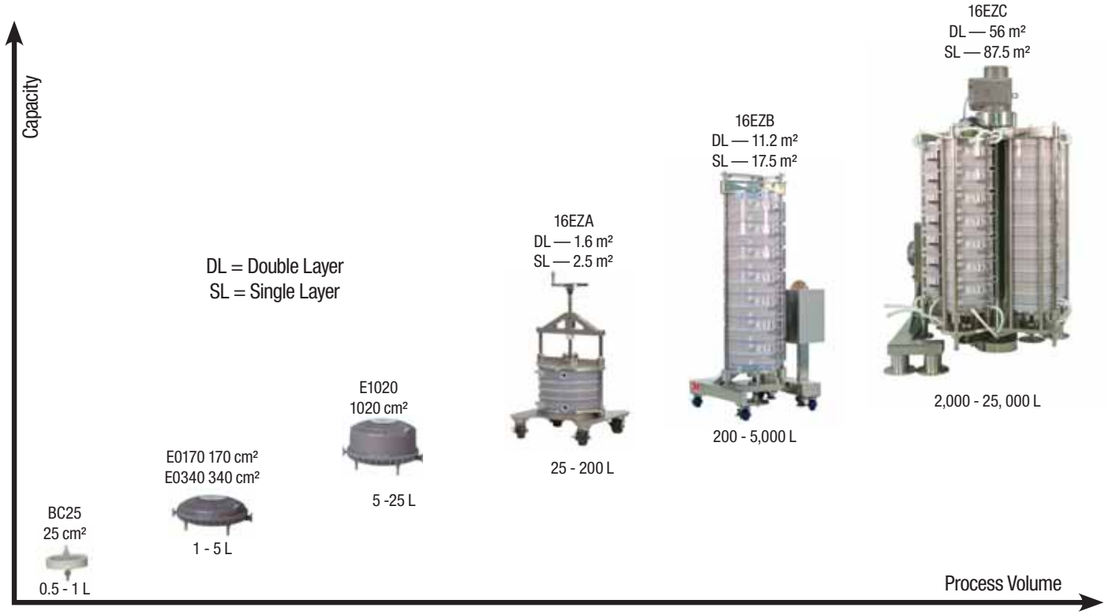
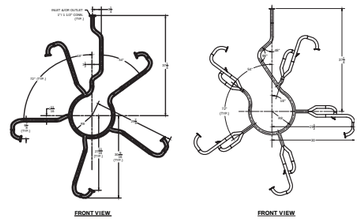


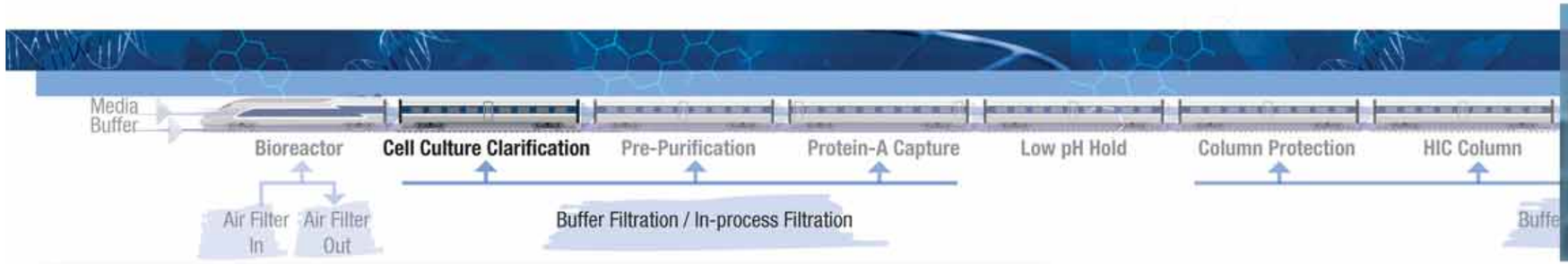
Figure 7: Scalable Single-Use Solutions from 0.5 to 25,000 liters

Accessories

Custom Single-use Tubing Connectors for Zeta Plus™ Encapsulated Systems



Staging Carts – For Loading Capsules



Zeta Plus™ Encapsulated Single-Use Products

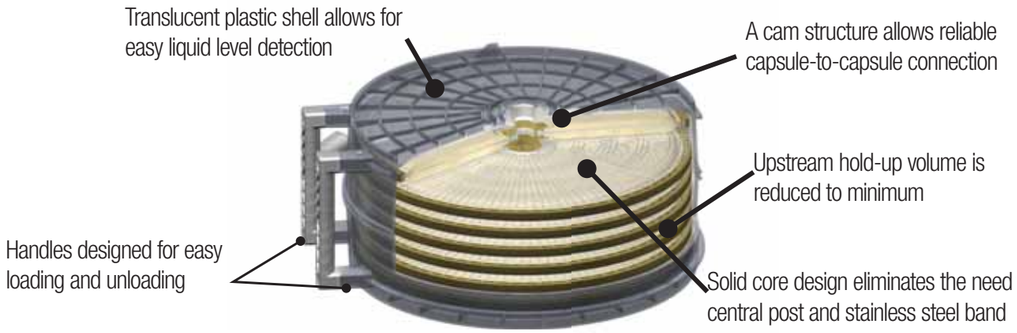
For Cell Culture Clarification

Zeta Plus™ Encapsulated Systems are designed to make cell clarification by depth filtration fast, easy and clean. 3M offers three models of Zeta Plus Encapsulated Holders — 16EZA, 16EZB and 16EZC — as a convenient single-use depth filter system for cell culture clarification. Both the Single Round (Model #16EZB) and Multi-Round (Model #16EZC) can be pivoted between horizontal and vertical positions, allowing for convenient loading and unloading, minimal footprint during filtration, minimal fluid spills during unloading, and full utilization of the filter media. The pilot scale system, 16EZA, uses up to 3.2 m² of depth filter media and is not designed to pivot.

Advantages of The Zeta Plus™ Encapsulated system

- Simplifies the operation of depth filtration step
- Full utilization of the filter media, small footprint during filtration
- Avoids spills on the manufacturing floor
- Ergonomic and saves labor

At the heart of the Encapsulated Zeta Plus system is the uniquely designed Depth Filter Capsule.



Zeta Plus™ Encapsulated Capsule With Standard Polycarbonate Shells

Zeta Plus™ Encapsulated Capsule With Alkaline Resistant* Polyphenylene / Polystyrene Shells

Table 3: Zeta Plus™ Encapsulated System Specifications

	16EZB	16EZC
Dimensions (nominal)	1.0 m x 0.5 m x 2.2 m (39.4" x 19.7" x 86.6")	2.9 m x 2.5 m x 2.2 m (114.2" x 98.4" x 86.6")
Carriage Array Options	1 rack of capsules	3 or 5 racks of capsules
Loading per Rack	1 - 7 capsules	7 capsules
Flexibility	Can plumb for two stage depth filtration in the same system (maximum number of capsules - 6)	Can load just one rack and leave others empty. Can plumb for two stage depth filtration
Torque Limiter	Manual	Manual (interlocked by PLC to ensure capsules are secure)
Indexing and Pivoting to Vertical Position	No indexing. Pivot by manual gear.	Automated with torsion limited electric motors.
Control	Manual - All mechanical parts	PLC controlled
Filter Area Double Layer Media Single Layer Media	 up to 11 m² up to 17.5 m²	 up to 55 m² up to 87.5 m²

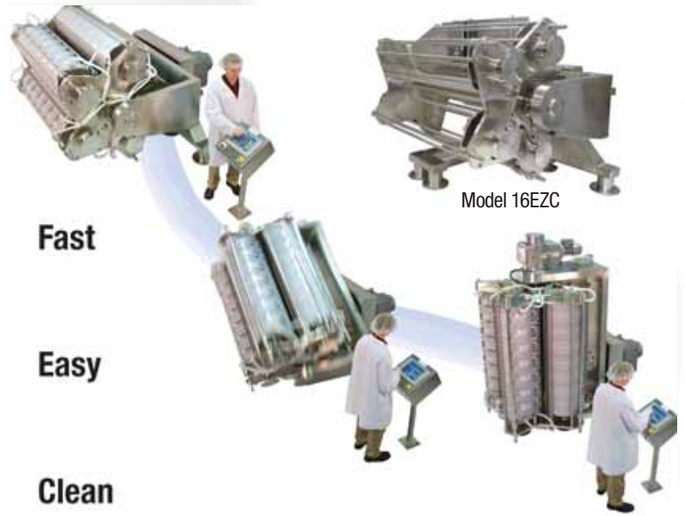
* Based on testing with 1M NaOH and 5% NaClO (Bleach). See Chemical Compatibility Guide (70-0202-2023-5/LITPHG03) for more information.

Zeta Plus™ Encapsulated System (Model 16EZB)

For up to 5,000 Liters

Zeta Plus™ Encapsulated Multi-Round System (Model # 16EZC)

For up to 25,000 Liters



Replacing a centrifuge in CHO cell harvest process†

The Zeta Plus™ Encapsulated single-use system has been used to replace a centrifuge and a conventional single layer depth filter in an existing process for CHO cell culture clarification at a major biopharmaceutical manufacturer.

Justification:

During harvest runs, the continuously stacked disc centrifuge broke down periodically, causing maintenance and operational bottle necks. Going from two-unit operations to one and converting a hard plumbed system into a single-use process results in significant savings.

Solution:

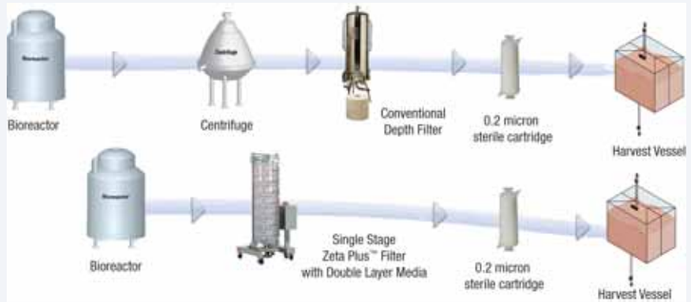
3M's Zeta Plus EXT media grade 60SP02A in an encapsulated format

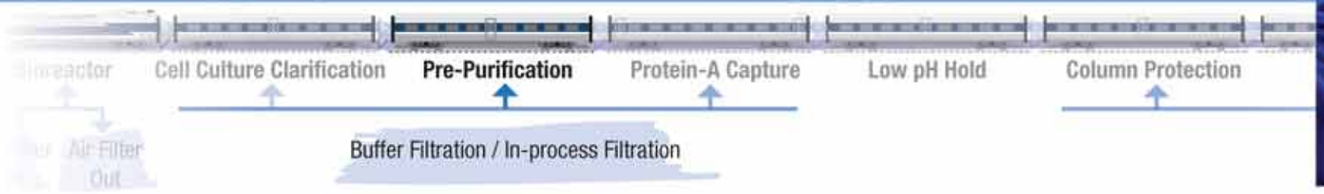
Details:

11 m² of Zeta Plus Encapsulated module processed 1,000 liter batch and differential pressure across the downstream 0.2 µm membrane was < 2 psid (0.15 bar) throughout the run

Operator Feedback:

- Minimal residual liquid was observed during system break-down.
- Zeta Plus Encapsulated system was easy and convenient to set up.
- Single-use depth filtration significantly reduced cleaning time for equipment and the process suite.
- No CIP or cleaning validation studies were required.
- Further, the cycle times were shortened thus reducing manufacturing costs.





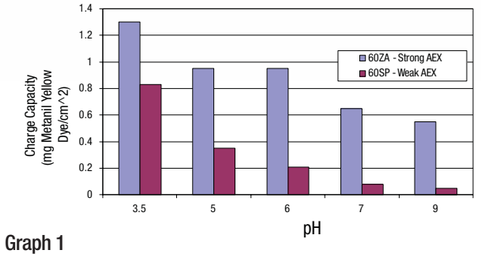
Exploiting The Charge Effect Of Depth Filters†

Depth filters are made of cellulose fibers, a filter aid (e.g. Perlite) and binding resins that impart a charge to the filtration matrix. 3M offers a range of depth filter matrices that have strong anion exchange (ZA grade media) to weak anion exchange (SP grade media) characteristics.

Monoclonal antibodies (mAbs) typically have isoelectric points (IEP or pI) that vary from pH of 4.5 to 8.5[1]. If the pI of the mAb is greater than the pI of the HCP/DNA contaminants, these contaminants can be removed by exploiting the operating pH and choosing the optimal depth filter resin system. It is important that the feed stream be relatively free of colloidal particles as they are also adsorbed by the charged depth filter.

Graph 1 above shows charge capacity of strong anion exchange and weak anion exchange resin as a function of pH. The graph shows Zeta Plus ZA (strong anion exchange [AEX]) maintains the charge at higher pH, while Zeta Plus SP (weak AEX) has reduced charge capacity as pH increases. DNA Removal at a pH 7.4 and 9.0 for Zeta Plus SP grade filters is shown in Table 4.

Zeta Plus SP grade depth filters have lower AEX capacity at pH 9 compared to pH 7.4.



Graph 1

Table 4: Percent Capture of DNA by Charged Depth Filter Media

Zeta Plus™ 90SP Grade Media Lot Number	% Removal of DNA	
	pH 7.4	pH 9.0
24022	99.9	29
24107	100.0	45
23443	99.8	68

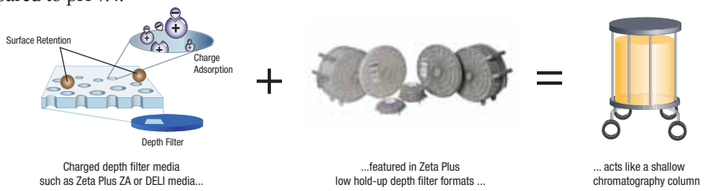
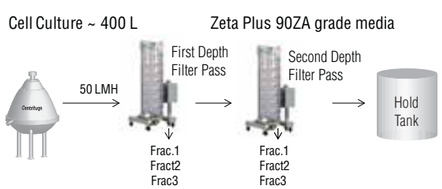


Figure 8:

Host Cell Protein Removal†

Host Cell Proteins (HCPs) are undesired components in down stream protein purification processes. HCPs are known to foul Protein A resins, thereby impacting the operation of this important purification step. In addition, the presence of high levels of HCP may lead to protein precipitation, or aggregation, either before or after the Protein A column. Low pH viral inactivation is particularly prone to protein precipitation. Protein aggregates can sporadically plug the sterile filters.



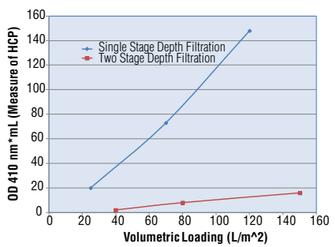


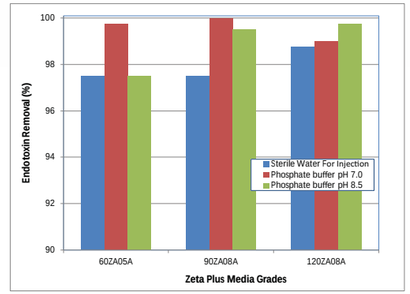
Figure 9 shows, the flow schematic and levels of HCP removal using Zeta Plus™ 90ZA depth filter media[2].

- Depth filter media grade 90ZA used in first and second pass
- Filtrate fractions were processed with a small scale Protein A column to assess turbidity and HCP elution

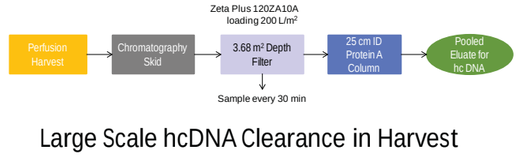
Figure 9: HCP Removal by Charged Depth Filters

Endotoxin Removal†

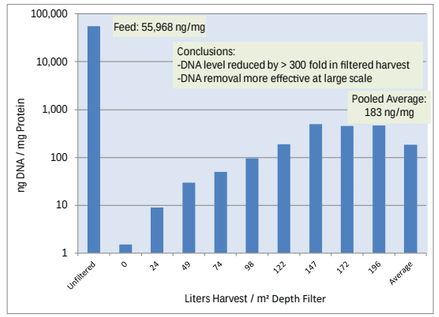
Endotoxins are cell wall components of gram-negative bacteria consisting of lipopolysaccharides that can cause a pyrogenic response in a parenteral formulation. When a protein therapeutic is made in a bacterial expression systems, such as *E. coli*, downstream processes are required to remove these endotoxins below the threshold level. Fortunately, because of its high negative charge, endotoxin can be removed using media that have anion-exchange characteristics. Graph 2 shows, endotoxin removal of various Zeta Plus grades filters[3].



Graph 2



Large Scale hcDNA Clearance in Harvest



Reference: Reduction of Host Cell DNA in Mammalian Cell Culture Using Charged Filters at Protein-A Capture for Monoclonal Antibod John Wesner Associate Scientist Development Pilot Plant Recovery Operations, Centocor R&D in BPI Korea 2008

Graph 3

DNA Removal

Downstream processes are required to reduce the residual host cell DNA to levels less than 100 pg / dose of the final protein therapeutic formulation per safety requirements of US FDA. Relatively high levels of DNA are seen in perfusion harvest and large amount of DNA co-elutes with the protein from the Protein-A column. The challenge for the downstream purification process is to consistently reduce DNA levels in the final product. DNA can bind nonspecifically to the backbone of Protein A column. Due to its phosphate groups, DNA is highly negatively charged at physiological pH and thus is well suited to be removed by binding to AEX ligands[4].

Zeta Plus™ depth filters can be used for DNA removal. Graph 3 shows Zeta Plus ZA media's DNA removal properties.

Product Recommendations For Pre-Purification Applications†

Choice of Media	Anion Exchange Functionality
LA, LP, SA & SP Grades	Tertiary Amine
ZA Grade	Quarternary Amine

Filtration Grade	Pore Rating
30	5.0 - 1.5 µm
60	0.8 - 0.2 µm
90	0.5 - 0.1 µm
120	0.3 - 0.1 µm

Single-Use Format	Effective Area
BC25	25 cm²
Scale-Up Capsule	170 cm², 340 cm², 1020 cm²
Small Zeta Plus™ Encapsulated	0.23 m²
Large Zeta Plus™ Encapsulated	1.6 m²

Application	Notes
HCP	• Flow Rate - 50 LMH • Typical Depth Filter Capacity 150-200 L/m² • Two stages work better than single
DNA Removal	• Flow rate -- 100 LMH • At Neutral and low pH DNA has a net negative charge
Endotoxin Removal	• Removal varies as a function of endotoxin challenge levels, type of solution (WFI, buffer etc.) and operating pH

Chromatography Column Protection

Particulate Removal prior to Chromatography Columns†

In biopharmaceutical downstream processes, protein refolding is effected by adjusting the pH and salt concentration of the feed solution. However, an undesirable by-product of this refolding process is the resultant particulate precipitates, or aggregates. Presence of particulates in chromatography feeds can result in plugging, fouling or loss of performance of the column. 3M's depth filter media can be used to remove particulates prior to Cation Exchange (CEX) or Anion-Exchange (AEX) column steps.

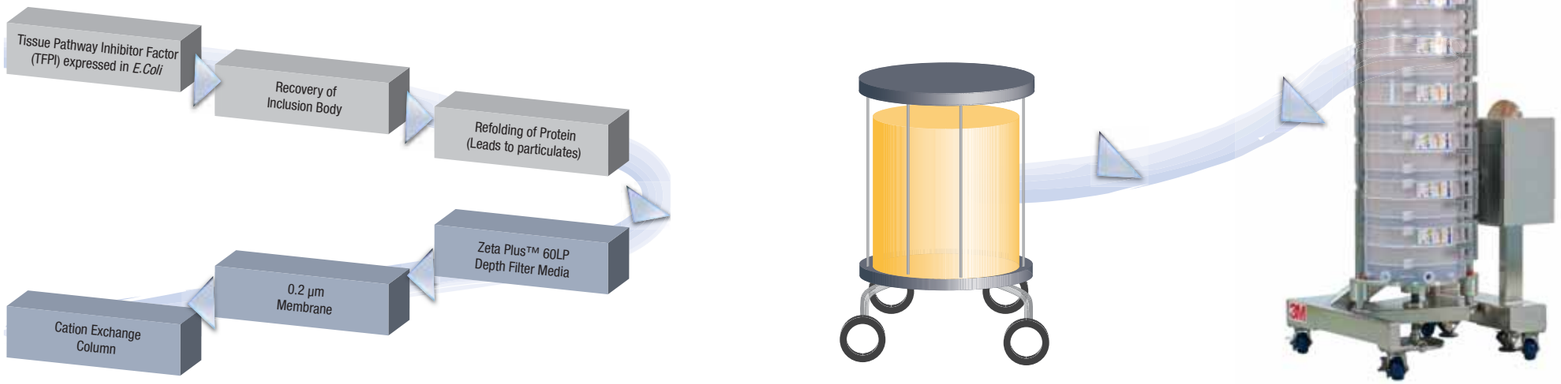


Figure 11: Particulate Removal Prior to CEX[5]

Improving Hydrophobic Interaction Chromatography (HIC) Column Performance†

Zeta Plus™ DEL series filters combine high lipid removal with cellulose-based depth filtration and can remove hydrophobic components and particulates such as lipids, protein aggregates and cell debris in a single step prior to a HIC unit operation[6]. Table 5 shows the effect of pre-treatment with Zeta Plus DEL series filter prior to an HIC column and the resultant improvement in performance.

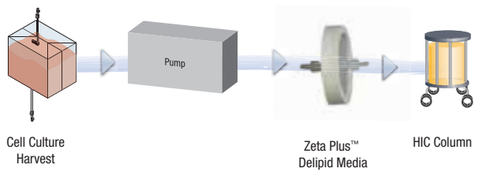


Figure 12: Improving HIC Column Performance

Table 5: HIC Performance with and without Zeta Plus™ DEL Series Media Pre-treatment (Loading volumes were adjusted to contain the same Virus-like Particle (VLP)* per cycle and equivalent percentage lipid amounts were calculated)

			Feed to HIC Column Pretreatment	
			No Filter	Zeta Plus™DEL Series Filters
	Lipid in the Feed		100%	43%
VLP Amounts in HIC Column	First Cycle	Loading	33%	80%
		Elution	93%	90%
		Yield	31%	72%
	40th Cycle	Loading	62%	87%
		Elution	29%	43%
		Yield	18%	37%

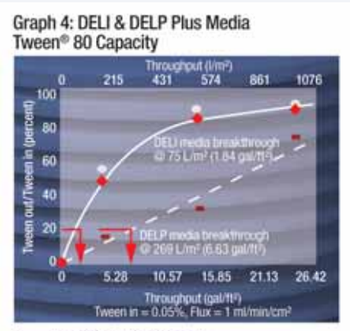
*Lipid foulant interactions during chromatographic purification of virus like particles from *Saccharomyces cerevisiae* , Ph D. Thesis, Jing Chin, 2010, University College, London

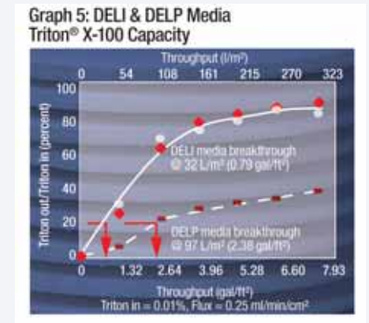
Zeta Plus™ Media and Selection Recommendations†

- Zeta Plus™ depth filters are used to remove particulates prior to chromatography columns
- Zeta Plus DEL series filter media contains activated silica that selectively adsorbs lipids, detergents, anti-foams that foul chromatography resins ultrafiltration (UF) systems and sterile membrane filters

Zeta Plus Media Choices and Selection Recommendations

Two different types of Zeta Plus DEL series filter media are available to suit varying application requirements. The chart below serves as a guideline for selecting the appropriate media type:





Type	Lipid Reduction Capacity	Optimized for Low Aluminum Extractable Levels	Optimized for Sensitive LAL* Test Procedures
DELI	Intermediate	No	No
DELP	High	Yes	Yes

**Limulus* Amoebocyte Lysate

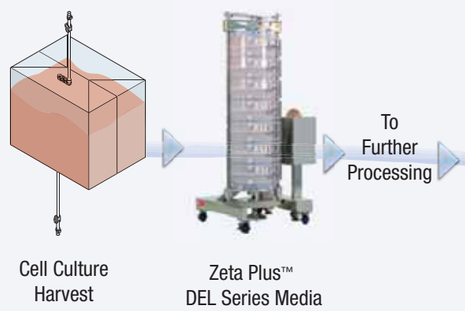
Anti-foam removal from cell-culture solutions†

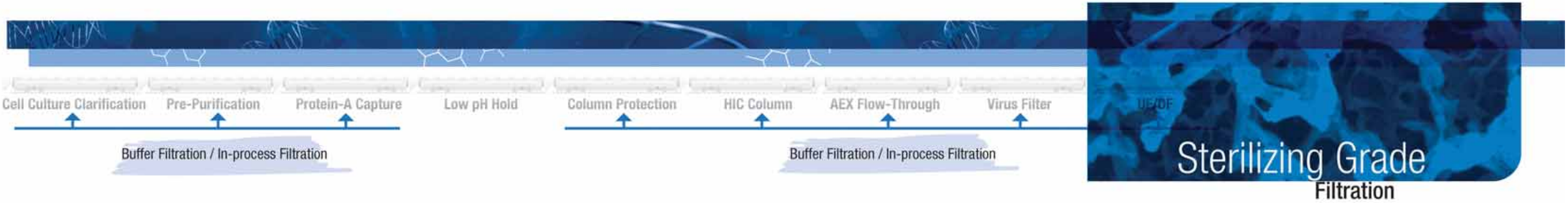
Application Details

- Anti-foam agents (e.g. Sigma Aldrich Antifoam A, silicone polymer, Dow 'Antifoam C')
- Typical concentrations 1-50 ppm
- Not cleared in chromatography steps, co-elutes
- Anti-foams foul downstream chromatography columns, UF and sterile membranes

3M Solution

- Zeta Plus Series Filter Media: contains hydrophobic/ lipid selective adsorptive media, cationic resin and cellulose





PES — The Preferred Membrane For Biopharmaceutical Applications

- Polyethersulfone (PES) membranes offer higher flow rates
- Broad chemical compatibility
- Wide pH range: Same filter for acid and basic buffers
- Low protein binding and adsorption

Sterilizing grade filters are widely used in many downstream processing steps. In addition to the sterile filtration prior to the final filling step, sterilizing filters are used widely in many intermediate steps to reduce cross-contamination risk from in-process liquids such as buffers. Cell culture growth media are filtered using 0.1 µm filters to mitigate the risk of mycoplasma contamination. Since biopharmaceutical unit operations are discontinuous in nature, elution pools (e.g. Protein A pool) need to be filtered with 0.2 µm filters prior to storage in order to manage bioburden loads. To prevent growth of microorganisms in downstream chromatography steps, post depth filter permeate is filtered using 0.2 µm sterilizing or bioburden reduction grade filters. Performance characteristics of LifeASSURE™ PDA PES membranes in various biopharmaceutical fluids are shown in graphs 6, 7 and 8.

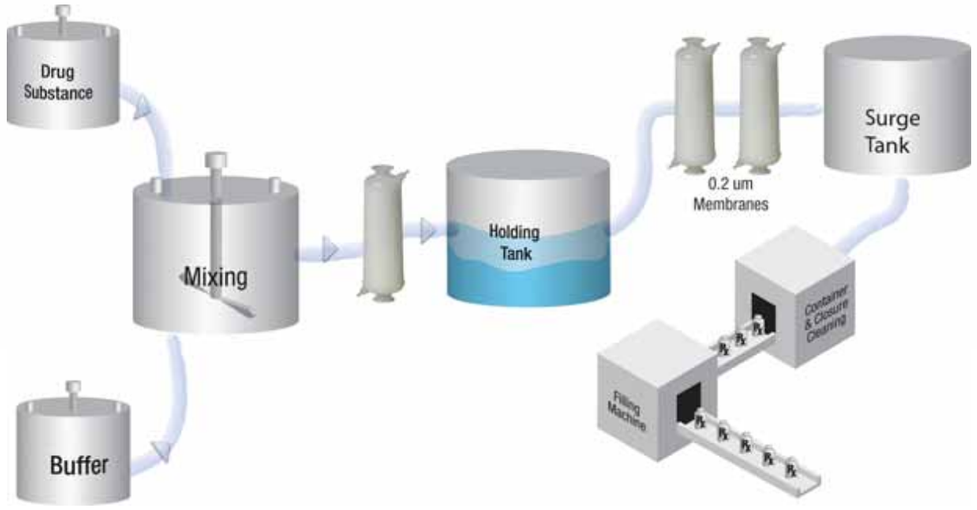


Figure 13: Biopharmaceutical — Sterile Final Filtration and Filling Process

3M Sterilizing Grade 0.2 µm Membrane Filters:

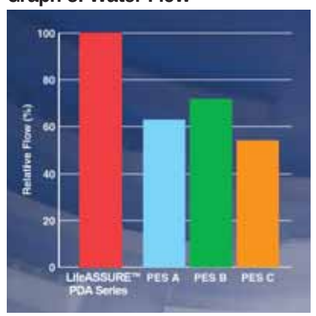
- LifeASSURE™ PSA—Nylon
- LifeASSURE™ PFS—PTFE
- LifeASSURE™ PDA—PES

50 mm Capsule Filters For Small-Scale Sterilizing Grade Liquid Filtration

Table 6 Comparative Choice Of Membranes†

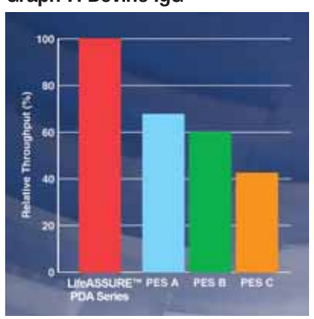
	Nylon	PES	PTFE
Strengths	• Good wettability • Positive charge • Lower rates of false integrity test (IT) failure	• High flow rates • Great throughput • Low and high pH compatibility • *Gamma* stable • Low protein adsorption	• Hydrophobic • Solvent stable
Weakness	• Lower flow rates • Low pH compatibility • Nonspecific adsorption • *Gamma* tolerance	• Wettability • Need to autoclave / steam wet	• Difficulties conducting integrity tests, such as the need to wet the membrane with alcohol
Lead applications	• Many cytotoxic drugs, • LVP applications	• Biotech products • Buffer / media filtration	• Critical vent filtration • Solvent / Sterile API applications

Graph 6: Water Flow



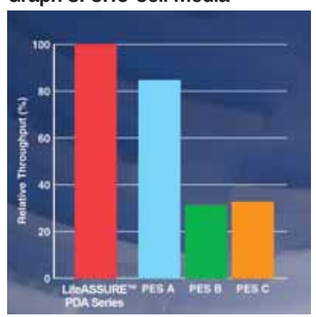
Relative water flow of 10 inch LifeASSURE™ PDA and commercially available PES cartridge filters. PES A, B, C cartridges water flow from product literature.

Graph 7: Bovine IgG



Relative throughput of bovine IgG (50 mg/ml) with equal area polyethersulfone membrane. Relative filtrate volume after 10 minutes at 15 psi feed pressure was measured.

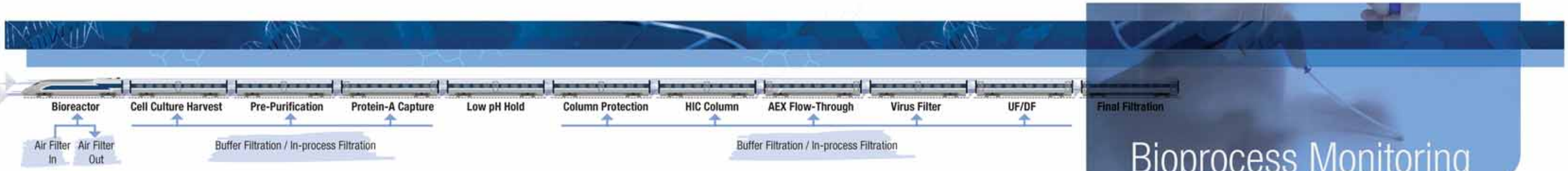
Graph 8: CHO Cell Media



Relative throughput of CHO cell media feed with equal area polyethersulfone membrane. Tests were conducted at a constant flow and throughput volume was measured at a terminal pressure of 25 psid.

Table 7: 3M Membrane Choices For Sterile Filtration Applications†

Membrane	3M Product	Pore Size	Applications	Additional Features
Polyethersulfone (PES)	LifeASSURE™ PDA Series Filters	0.6 / 0.2 µm Two Layers	• Final Filtration • In-process Filtration • Filtration of chromatography pools • Post-depth filter sterile filter • Buffer filtration	• Capsules in *gamma* pre-sterilized version available • Sterilizing Grade Filter • Rated to remove 10^7 *B. diminuta* per ASTM ASTM F838-05 tests • 100% integrity tested prior to release
Polyethersulfone (PES)	LifeASSURE™ PNA Series Filters	0.2 µm Single Layer	• Bioburden reduction applications • In-process filtration	• Bioburden reduction filter • Membrane is rated to >7 LRV for *B. diminuta* • 100% integrity tested prior to release
Nylon 66	LifeASSURE™ SP Series Filters	0.2 µm Charged Modified	• Retention of negatively charged particulate contaminant including endotoxins • Suitable for removal of endotoxins in water at point of use	• Sterilizing Grade Filter • Rated to remove 10^7 *B. diminuta* per ASTM ASTM F838-05 Tests • 100% integrity tested prior to release
Nylon 66	LifeASSURE™ PSA Series Filters	0.1 µm	• Rated to provide LRV 7 of mycoplasma while providing good flow rate	• Validated 0.1 µm membrane that provides reliable retention of mycoplasma • 100% integrity tested prior to release
PTFE	LifeASSURE™ PFS Series Filters	0.2 µm	• Sterile air venting and filtering applications • Liquid validation of *B. diminuta* retention to provide reliable sterilizing performance in wet or dry conditions • Demonstrated complete aerosol retention of the bacteriophage ΦX-174	• Sterilizing Grade Filter • Rated to remove 10^7 *B. diminuta* per ASTM ASTM F838-05 Tests • 100% integrity tested prior to release

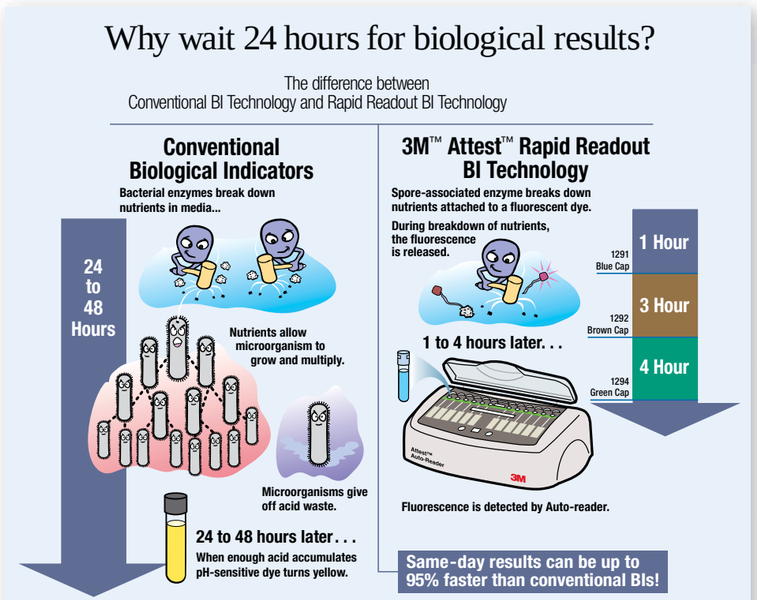


Bioprocess Monitoring Applications

3M makes innovative products for biopharmaceutical monitoring applications. 3M Comply™ chemical indicators can provide a visual 'Accept' / 'Reject' for steam sterilization. Our innovative Attest™ Rapid readout biological indicators can provide rapid results when using biological indicators-while simultaneously avoiding aseptic transfers, and the need to prepare media. Clean-Trace™ technologies use ATP monitoring to test for biological activity on surfaces and to validated the cleaning process. 3M Pertrifilm Aqua Plates are suitable for efficient monitoring of plant's water.

3M™ Attest™ 1292-S Rapid Readout Biological Indicators and 3M™ Attest™ Auto-readers

- Provide final readout in 3 hours to validate steam sterilization applications
- Self-contained biological indicator design reduces risk of contamination during transfer
- Recognized by the US Food and Drug Administration as a biological indicator
- Auto-reader has either 12 or 36 vial capacity and provides automatic calibration on every biological indicator



Chemical Integrators For Monitoring Steam Sterilization

- "Accept" or "Reject" at a glance
- For use in all 118-138°C (245-280°F) steam sterilization cycles
- Conform to ANSI/AAMI/ISO 11140-1:2005 and EN ISO 11140-1:2005 Class 5 Integrating Indicators
- Identify non-sterile instruments before they enter the sterile field

3M™ Clean-Trace™ Technologies

- ATP indicates biological residues — food, bacteria, body fluids
- ATP tests are fast — as little as 30 seconds
- Easy to use hardware and software

Proven Real-Time Results You Can Rely On To Make Critical Business Decisions

- Consistent and repeatable results with high levels of sensitivity demonstrated in independent studies
- Used around the world by leading food and beverage manufacturers as an integral part of their HACCP plans
- Can be tailored to suit requirements of large manufacturing facilities or smaller laboratories

Increased Operational Efficiencies

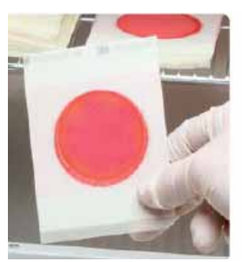
- Powerful data trending software supplied with the 3M™ Clean-Trace™ NG Luminometer instrument to easily track and improve hygiene performance over time
- Provides information to optimize cleaning regimes which can generate savings in cleaning materials and labor requirements
- Helps create production environment conditions conducive for maximizing shelf life of products

3M™ Petrifilm™ Aqua Plates for Water Testing

3M™ Petrifilm™ Aqua Plates are sample-ready media that replace conventional agar, petri dishes, media pads and disposable filter funnels used in the microbial testing of water. Each plate contains a water-soluble gelling agent, nutrients and indicators in a dry, shelf-stable format.

We offer four 3M Petrifilm Aqua Plates to cover your unique testing needs:

- Heterotrophic Count
- Coliform Count
- Enterobacteriacea Count
- Yeast and Mold Count

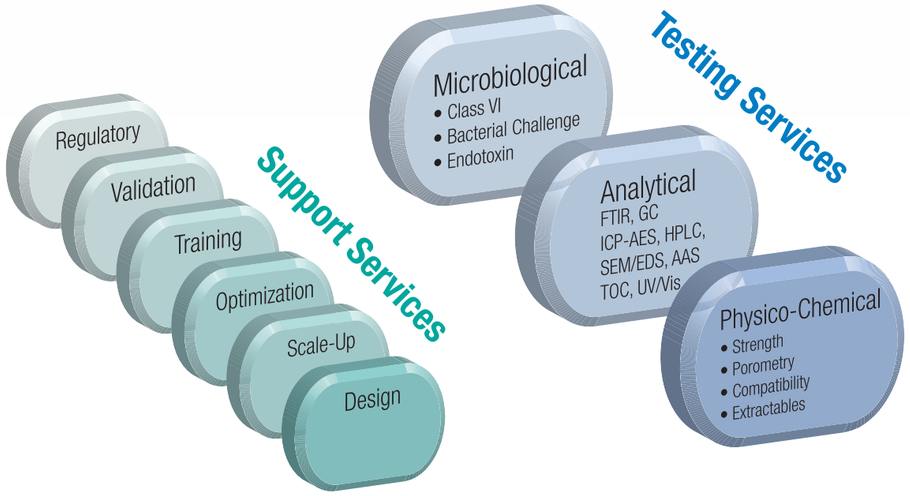


Advantages:

- 80% increase in productivity
  - Ease of use
  - Compatible with membrane filtration
- 85% savings in storage space (50 3M Petrifilm Aqua Plates vs. 50 agar dishes and 50 disposable filter funnels)
- Confirmed coliform results in just 24 hours
- Longer shelf life vs premade agar plates

Scientific Applications Support Services (SASS)

3M has a global team of market-focused scientists and engineers who excel in supporting, collaborative efforts between our customers and 3M. Our technical team is skilled in performing on-site bench-scale tests and relating their results to full scale manufacturing filter operations. When unique processing problems are encountered, our expert product and application specialists are equipped to identify ~~filter~~ solutions using either 3M's broad array of existing products or work directly with our customers to design a custom solution for the job.



Validation Services

3M provides the following validation and scientific services for the biopharmaceutical industry from its various regional global technical service centers.

Post-use Integrity Test
- **GMP Guidelines**
- **Process Fluid**
- **Safety Margin**
- **Correlation**

Bacterial Challenge Test
- **ASTM**
  - *B. Dimunuta* ATCC 19046
- **HIMA**
  - Procedures
- **GMP Guidelines**
  - Process Operating Conditions
  - Worst case
    - *Minimum Qualifying Standards*
  - Grouping / Bracketing
  - Correlated Integirty Tests
    - *Filter manufacter's initial qualification*

Compatibility
- **Sterilization**
- **CFR**
- **USP**
- **Integrity**
- **Hardware**

Adsorption
- **GMP Guidelines**
- **Binding**
  - Preservatives
  - Equilibrium
  - Saturation
  - Recovery

Extractables
- **Flushing**
  - Biological Safety
  - USP
- **Toxicity**
- **Identity**
  - Permitted materials
- **GMP Guidelines**
- **Flushing**
  - CFR
- **Quantity**
- **Active Materials**

3M Purification provides comprehensive technical services and advanced engineering support for biopharmaceutical customers from centers around the world.

End Notes

1 King, David. *Applications And Engineering Of Monoclonal Antibodies.* Philadelphia, PA: Tyler & Franics Inc., 1998. Print.

2 Yigzaw, Yinges; Piper, Robert; Tran, Minh; and Shukla, Abhinav A. "Exploitation of the Adsorptive Properties of Depth Filters for Host Cell Protein Removal during Monoclonal Antibody Purification." *Biotechnology Progress.* 2006: 22, 288-296. Web.

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5 Dorin, Glenn J. et al. (2001) *Method of solubilizing, purifying, and refolding protein.* US Patent 6,319,896. Page 46-47.

6 Lin, Jing. "Lipid Foulant Interactions During Chromatographic Purification of Virus Like Particles (VLP) from Saccharomyces Cervacie." Ph D Thesis, University College London, Sept 2010.

† The information presented here contains data and conclusions from studies where process conditions of filtration and separation technology was optimized by the respective researchers. Each application of filtration and separation technology may have significant process differences and it is important for the user to conduct similar process and scale-up studies to validate performance in a particular application. Please contact 3M Purification's global SASS team for help with specific applications.

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