NatriFlo® HD-Q Data File

Executive Summary

The NatriFlo HD-Q Membrane is an advanced material with a three-dimensional macroporous hydrogel structure that provides High Density of binding sites and rapid mass transfer. Natrix HD Membranes deliver binding capacity that exceeds resin-based columns with fast flow-rates typical of membrane adsorbers. This combination of performance and speed enables:

- Best-in-class HCP removal, DNA removal and Viral Clearance, even with the most challenging feed streams and plenty of capacity to spare
- Salt and pH tolerance in an industry-standard strong anion exchange (Q) chemistry (even in phosphate buffer systems)
- Simple, low cost polish operations in a single-use format

The combination of extremely high functional group density, multi-point binding of biomolecules, and rapid mass transfer, give the NatriFlo HD-Q membrane best-in-class polish performance. NatriFlo HD-Q membranes can be loaded equal to or higher than competitive membranes and an order of magnitude higher than resins. This higher loading is feasible even with feed sample conductivity as high as 15 mS/cm. High binding capacity and superior throughput combined with improved salt tolerance of Natrix HD-Q membranes provides development flexibility and increased process robustness, which translate into improved process economics.

This document highlights performance data for key aspects of the NatriFlo HD-Q flow-through membrane. The data reflects testing done by downstream scientists at several leading commercial biopharmaceutical organizations.

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NatriFlo® HD-Q Summary

NatriFlo HD-Q is a high capacity, high throughput strong anion exchange membrane adsorber designed to purify biomolecules, such as monoclonal antibodies (mAbs), in flow-through operating conditions. The unique Natrix HD-Q membrane contains a high density of quaternary amine ligands that are directly polymerized within the porous membrane scaffold. The interconnected pore structure and high ligand density of the HD-Q membrane at the heart of the NatriFlo HD-Q adsorber enables fast flow rates with impressive throughput to extremely high loads (>10 kg per liter of membrane for some mAbs) and maintains excellent impurity reduction at these extreme operating conditions. The NatriFlo HD-Q design delivers improvements in productivity, flexibility, and process robustness for any bioprocess design.

Key benefits of NatriFlo HD-Q

- Best-in-class host cell protein (HCP) removal, DNA removal and Viral Clearance, even with the most challenging feed streams...with plenty of capacity to spare
- Salt and pH tolerance with strong anion exchange (Q) chemistry (even in phosphate buffer systems)
- High-capacity final polish purification with extreme protein throughput (>10 kg/L)
- Scalable, easy to optimize purification solutions at high-throughput
- Increased operating flexibility due to a large window of protein loading, flow rates (up to 25 membrane volumes (MV) per minute) and feed solution conditions
- Increased manufacturing productivity, decreased operation complexity, and improved robustness and process economy
- Simple, low cost polish operations in a single-use format
- Stable and secure supply, validation and regulatory support

Figure 1: Natrix HD-Q Family

The NatriFlo HD-Q family (Recon, Pilot & Process devices shown) offers scalable polishing from R&D to cGMP manufacturing.

Natrix HD-Q membrane characteristics

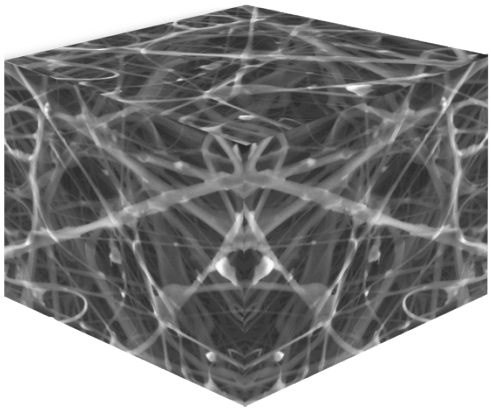
Ion exchange groups

The Natrix HD-Q membrane is a strong anion exchanger that contains a high density of quaternary amine group ligands (amidopropyl trimethylammonium chloride) chemistry that is well established in large-scale purifications.

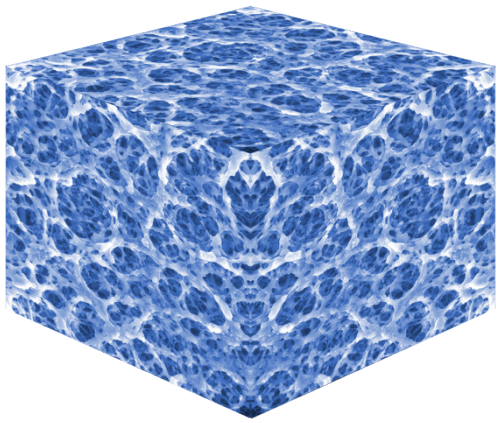
The Natrix HD-Q membrane is a porous polyacrylamide hydrogel containing a high density of pendant quaternary ammonium (Q) binding groups physically reinforced by an inert fiber web **(See Figure 2)**. The interconnected pore structure (nominal pore size 0.4 µm) provides a large surface area for protein binding and high permeability. This unique combination of high density Q hydrogel chemistry, high definition protein separation **(Figure 3)** and porosity produces a membrane with a very high binding capacity across a wide range of flow rates (see **Figure 4** for BSA versus flow performance and **Figure 5** for pressure versus flow performance). In combination with the well-established Q ligand chemistry, these features make Natrix HD-Q an excellent choice for reliable polishing in a commercial setting. See **Table 1** for a summary of membrane characteristics.

Figure 2: Structure of Natrix HD-Q membrane

Natrix HD-Q membrane is composed of a porous, functionalized 3-dimensional hydrogel polymerized within and around a flexible fiber web support.



Flexible polymeric support web physically reinforces functional hydrogel



Web is enclosed by and filled with porous functionalized hydrogel, establishing pore size.

Figure 3: Model Protein Separation on NatriFlo HD-Q Recon

This figure illustrates a very good separation of a mixture of four different proteins.

Flow rate 15 MV/min, separation of myoglobin (1), conalbumin (2), ovalbumin (3) and trypsin Inhibitor (4) using a conductivity gradient 0 to 500 mM NaCl.

Performance is comparable to column chromatography.

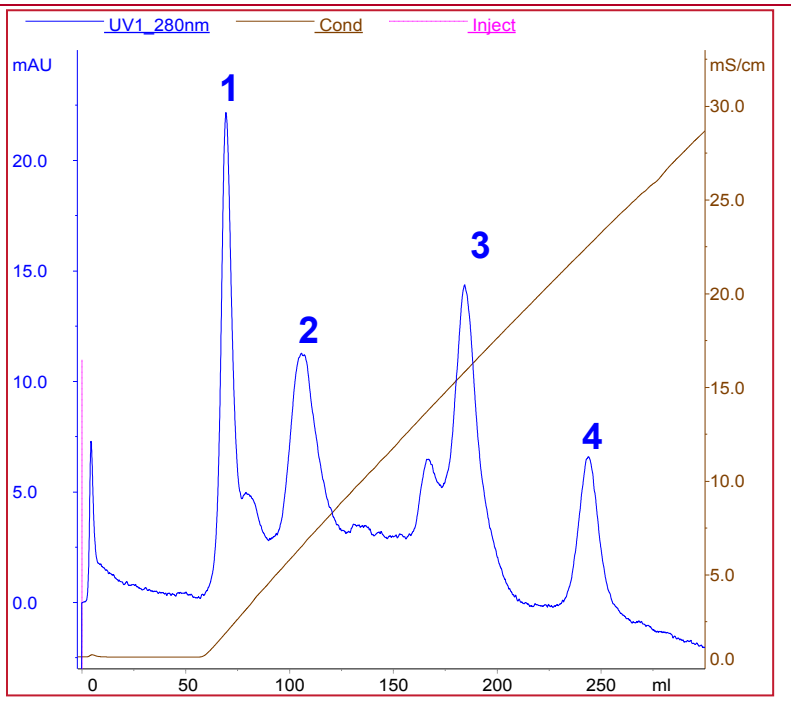


Figure 4: NatriFlo HD-Q Recon Binding vs. Flow characteristics

NatriFlo HD-Q achieves excellent dynamic binding capacity across a wide range of flow rates.

NatriFlo HD-Q BSA binding capacity versus flow curve was generated using equilibration buffer (25mM Tris, pH 8.1) on Recon device.

10 MV/min is considered the reference (100%).

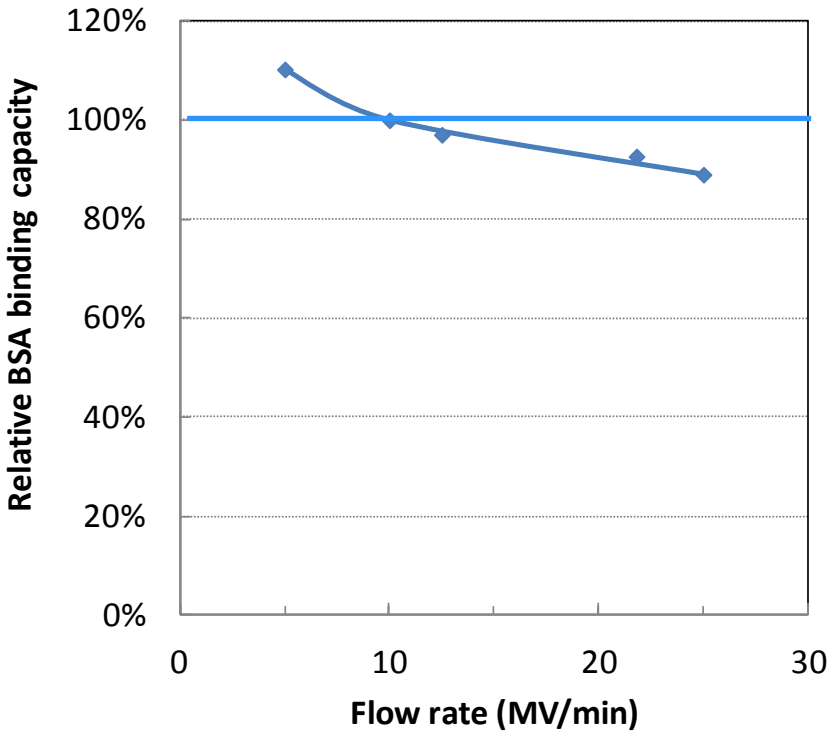
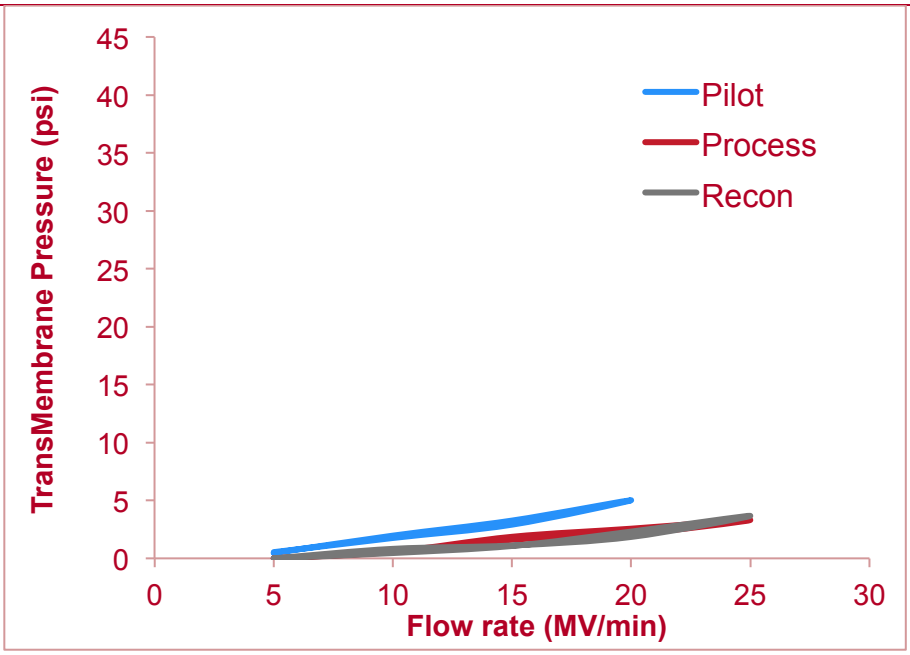


Figure 5: NatriFlo HD-Q Membrane Adsorber Pressure vs. Flow characteristics
Natrix HD-Q shows very little increase in trans-membrane pressure across a wide range of flow rates.

The curve was generated using equilibration buffer (25mM Tris, pH 8.1) on GE ÄKTA Explorer 100.



NOTE: The binding characteristics and low pressure inherent to NatriFlo HD-Q design enable operation at flow rates even higher than 25 membrane volumes per min (MV/min).

Table 1: Primary characteristics of Natrix HD-Q membrane

Hydrogel	Porous polyacrylamide
Functional group	Amidopropyl trimethylammonium chloride (quaternary amine)
Typical flow rate	5-25 MV/min
Nominal pore size	0.40 µm
BSA binding capacity	> 200 mg/mL
DNA binding capacity	> 20 mg/mL
Chemical compatibility	Compatible with most buffers and solvents commonly used in chromatographic biomolecule purification processes (see the Validation Guide for complete and detailed information)
Incompatible chemicals	Hypochlorite (1%); SDS (1%)
Shipment conditions	Dry, ready to use (free of preservatives or wetting agents)
Storage conditions	Store at room temperature prior to use

Operation and Performance

NatriFlo HD-Q membrane adsorbers are changing the way flow-through polishing operations are conducted. Binding capacities exceed that of resin-based columns with flow rates comparable to typical membrane adsorbers. In addition, NatriFlo adsorbers are a fraction of the size of their conventional resin counterparts for equivalent scale processes. The reduced footprint enables true single use deployment for downstream polishing operations. NatriFlo adsorbers are easily scalable from the laboratory to GMP production and are designed to work with existing chromatography systems.

High-Performance Protein Purification at Every Scale

The NatriFlo HD-Q product family (Table 2) offers scalable polishing solutions for efficient biomolecule purification.

Table 2: NatriFlo HD-Q Membrane Adsorber Properties

	PRODUCT NAME				
	Recon Mini	**Recon**	**Pilot**	**Process 150**	**Process 600**
Nominal membrane volume (mL)	0.2	0.8	15	115	460
Minimum standardized BSA binding capacity (g)	0.04	0.16	3	23	92
mAb nominal polishing @ 10 kg/L load (g)[1]	2	8	150	1150	4600
Membrane configuration	Flat sheet	Flat sheet	Pleated	Pleated	Pleated
Flow rate range[2]	1 - 5 mL/min	4 - 20 mL/min	75 - 375 mL/min	0.6 - 3 L/min	2 - 10 L/min
Intended use	Scaled down laboratory model to screen and fine-tune parameters. For limited quantities of protein.	Intermediate scale adsorber, intended to verify and adjust operating parameters. Processing capacity up-to 220g of mAb under cGMP		Process scale adsorber designed for full-scale GMP manufacturing of proteins.	

[1] Based on typical process streams and loading up to 10 kg mAb/L-membrane. Loading capacity is not limited to 10 kg/L and depends on the total impurity content

[2] Typical flow rate range is based on 5-25 membrane volumes/minute. Specific flow rates can be determined to accommodate process requirements (e.g. maximum back pressure, improved process time, etc.).

High Capacity Purification

The Natrix HD-Q membrane is highly efficient at capturing negatively-charged contaminants such as DNA, viruses, endotoxins and acidic host cell proteins found in process feed streams. For mAbs and other biomolecules, anion exchange chromatography is widely used as a flow-through polish step in process manufacturing. The amount of mAb load for this unit operation is dependent on the type and amount of impurities in the process feed, the binding capacity of the resin or membrane and its salt tolerance. The large size of traditional chromatography columns is due to poor throughput or flow properties of the resin (lower mAb/protein loads for a given flow rate). Also, current membrane chromatography cannot provide sufficient process robustness due to limited binding capacity and generally poor salt tolerance. However, the NatriFlo HD-Q membrane adsorber overcomes these limitations with high binding capacity and high flow rates to produce first-in-class performance. The following data show the excellent performance capability of Natrix HD-Q membrane.

Virus clearance

NatriFlo HD-Q membrane adsorbers have demonstrated excellent virus clearance at very high mAb loads (10kg/L) even at extreme flow rates (25MV/min). **Figure 6 and Figure 7** show clearance of two model viruses, xenotropic murine leukemia virus (xMuLV, retrovirus, enveloped, ssRNA, 80-120 nm) and murine minute virus (MMV, parvovirus, non-enveloped, ssDNA, 18-26 nm) from partially purified mAb feed stream by Natrix HD-Q membrane at pH 7.5.

The study was conducted at a viral testing facility (Lancaster Laboratories, Lancaster, PA) with a Natrix collaborator.

The mAb titer in the process feed sample was 15 g/L (with1.3% aggregates, 84 ppm HCP and 83 ppb DNA). Natrix HD-Q membrane achieved excellent clearance (≥ 4.8 LRV) of xMuLV virus from partially purified mAb feed sample over a wide conductivity (5 – 15 mS/cm) and flow rate (10 – 25 MV/min) at 10 kg/L load. The data reveals excellent salt tolerance for viral clearance for both viruses and flow rate independence for viral clearance with xMuLV, even at very high mAb loads. This result indicates process robustness through more available capacity for impurities thanks to a large excess of binding sites, multi-point binding and large available surface area.

Figure 6: The effect of flow rate and conductivity on xMuLV clearance

Natrix HD-Q achieves excellent xMuLV clearance over a wide range of flow rates and conductivity conditions.

Feed - 15 g/L mAb at pH 7.5 & 5 mS/cm conductivity.

Total virus cleared to ≥ value indicated (limit of detection) in all cases.

Note: The combination of 25 MV/min and 15 mS/cm was not tested.

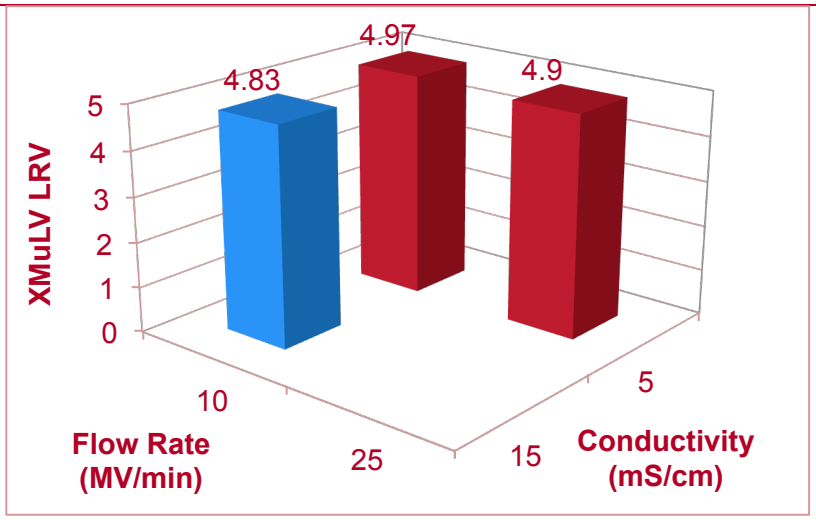


Figure 7. MMV clearance as a function of mAb load at different conductivities

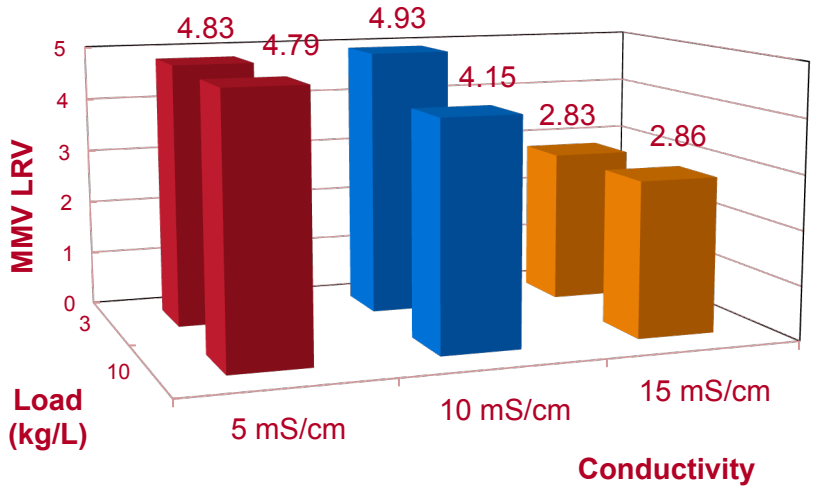
NatriFlo HD-Q demonstrates excellent MMV clearance across a wide range of protein loading and up to 10 mS/cm conductivity. Clearance is still good and as expected above 10 mS/cm.

At 5 mS/cm conductivity, MMV clearance remains constant (4.8 LRV) between load values of 3 to 10 kg/L;

At 3 kg/L load, MMV clearance remains same (4.8 LRV) from 5 to 10 mS/cm;

Feed - 15 g/L mAb at pH 7.5;

Flow rate – 10 MV/min



HCP clearance

The NatriFlo HD-Q membrane adsorber has demonstrated excellent HCP clearance capability across multiple mAb process feed streams. **Figure 10** shows collaborator HCP clearance data demonstrating the excellent performance of NatriFlo HD-Q even at high load conditions.

Figure 8 compares HCP removal capability of NatriFlo HD-Q membrane adsorber against two other competitive membrane adsorbers. The maximum acceptable HCP concentration for this particular mAb was 30 ppm. NatriFlo HD-Q-treated mAb solution did not cross this cut-off mark with load as high as 4 kg/L whereas other membrane adsorbers were only able to maintain the low HCP acceptance limit at less than 1.5 kg/L load.

Figure 8: HCP breakthrough for a comparative load up-to 4kg/L
NatriFlo HD-Q achieves better load capacity than competition for the same process stream.

Trial at collaborator.

HCP Clearance Specification Limit is 30 ppm.

Sartorius and Pall are beyond limit at 1.2 kg/L and <1.0 kg/L loading, respectively.

Natrix is still within limit at 4 kg/L.

Feed HCP: 104 ppm;

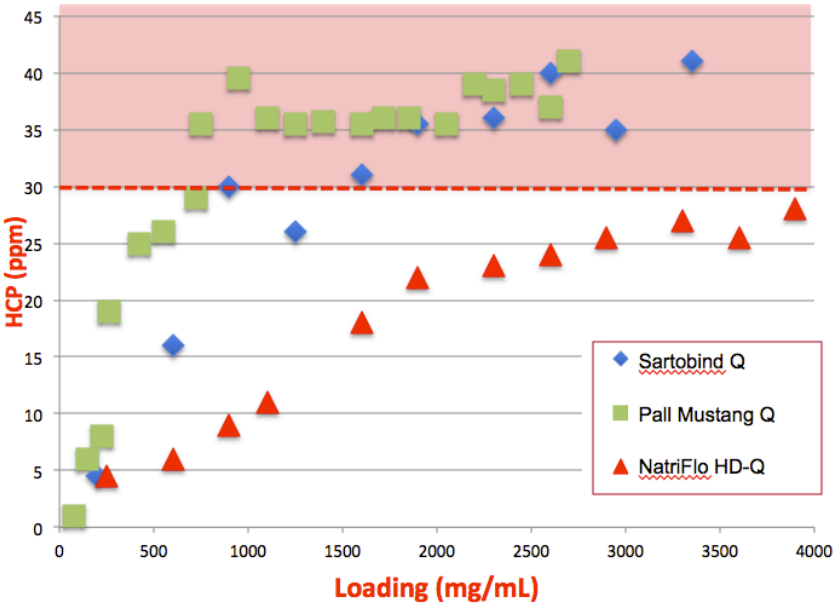
Feed DNA: 1.7 ppm,

pH 7.5,

Flow rate: 10 MV/min

Conductivity: 5 mS/cm.

Sartobind® Q is a registered trademark of Sartorius Stedim Biotech. Pall Mustang® Q is a registered trademark of Pall Corporation.



Another comparison evaluated HCP reduction for NatriFlo HD-Q compared to salt tolerant membrane adsorbers for a load containing high levels of HCP (**See Figure 9).** The Natrix HD-Q membrane reduced the HCP to < 50% whereas the other membranes had marginal performance for HCP reduction for this feed.

Figure 9: HCP clearance: Comparison of NatriFlo HD-Q with Chromasorb & STIC

NatriFlo HD-Q achieves good HCP reduction with a very dirty process stream (181,125 ppm) , showing a ~50% HCP reduction vs. virtually no HCP reduction for competitive products.

Trial at collaborator

Sample:

- *Conductivity 8 mS/cm*
- *pH: 7.5*
- *Flow rate: 10 MV/min*
- *Load 1 kg/L.*

STIC® is a registered trademark of Sartorius Stedim Biotech. Chromasorb™ is a trademark of Millipore Corporation.

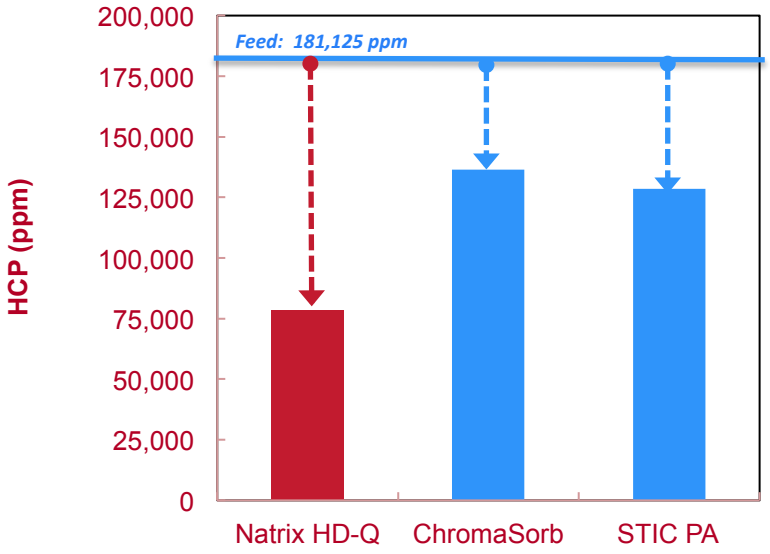


Figure 10 shows the HCP clearance capability of NatriFlo HD-Q membrane adsorber from protein A purified mAb at 10 kg/L load. The flow-through product was collected in 10 fractions, each correspond to 1 kg/L load. The constant level of HCP around 20 ppm in the first to last fraction clearly indicates the potential for good HCP clearance at very high loads (> 10 kg/L) on the NatriFlo HD-Q membrane adsorber.

Figure 10: HCP reduction performance for a load @ 10kg/L

NatriFlo HD-Q maintains consistent HCP reduction up to a high protein load, with apparent capacity to spare.

Trial at collaborator (Courtesy of Gallus BioPharmaceuticals)

The level of HCP measured corresponds to the non-binding impurities (pI close to or above the mAb pI).

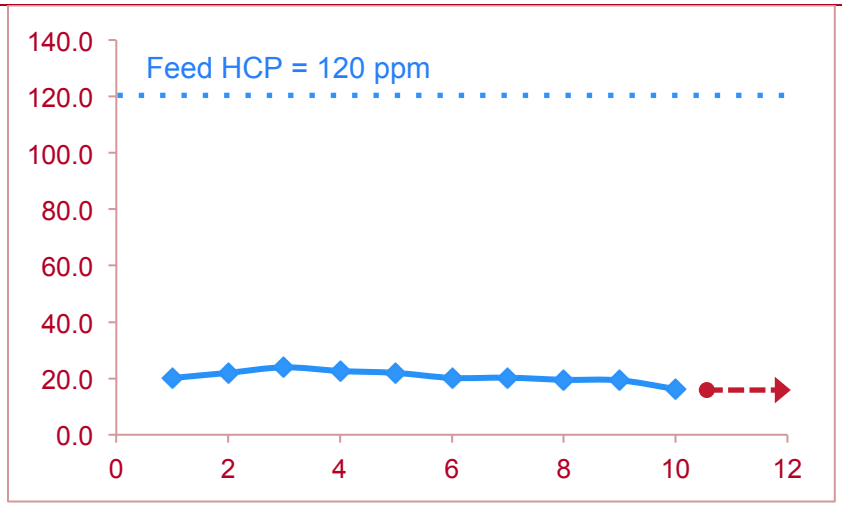
NatriFlo demonstrated very efficient clearance with no sign of increasing BT.

Equilibration Buffer: 20mM Phosphate with 100mM NaCl

pH: 7.0

Flow rate 10MV/min

Natrix Product: Recon



Endotoxin and DNA clearance

NatriFlo HD-Q membrane adsorber demonstrated excellent DNA clearance (>2.96 LRV) at 10 kg/L load from a mAb feed sample at a conductivity of 10 mS/cm. NatriFlo HD-Q reduced DNA levels in the mAb sample from 612 ppb to <0.7 ppb at 10 kg/L load (as measured by qPCR assay).

The Natrix HD-Q membrane has shown excellent endotoxin clearance (>4 LRV) from buffer (25 mM tris + NaCl, pH 8) spiked with endotoxin at concentration >1000 EU. This study was run using protein-free buffer since endotoxin can interact with proteins in a process-specific manner. The NatriFlo HD-Q membrane adsorber demonstrated >4 LRV for endotoxin loads as high as 9 million EU/mL of membrane at 5 and 15 mS/cm conductivity.

For additional detail, please see **Figure 13** Salt Tolerance and **Figure 18** in Scalability section.

Operating Flexibility

The equipment required to run the NatriFlo HD-Q adsorbers is the same as that used for typical chromatography columns. Further, NatriFlo HD-Q chromatography can also be performed by simply using a peristaltic pump if the chromatography skid is not available. The laboratory scale units can be attached with luer lock fittings to simple pump systems or more sophisticated chromatography equipment with multiple pumps and monitors. The Pilot and Process adsorbers accommodate either hose barb or sanitary fittings and can be attached to the high flow pump systems of chromatography skids currently used in GMP facilities, including the new ÄKTA Ready (GE Healthcare Life Sciences) flexible facility skids. Refer to the NatriFlo HD-Q Instruction Guide for further details and contact Natrix Separations or its authorized local distributor for any custom requirements for device connectors or for assistance with the installation and integration of NatriFlo HD-Q adsorbers to existing chromatography systems.

With a very high loading capacity, NatriFlo HD-Q adsorbers are the ideal option for flow-through polish applications. The average dynamic binding capacity of BSA (at 10% breakthrough) is >200 mg/mL of membrane at a flow rate of 10 MV/min. NatriFlo HD-Q has a demonstrated mAb throughput capacity of 10 kg per liter of membrane volume with no observed limit to further capacity (no observable HCP breakthrough at 10 kg mAb/L).

High salt tolerance

The very high binding capacity of Natrix HD-Q Membrane enables efficient operation over a wide range of solution conductivities.

For details on Salt Tolerance performance, please see **Figures 11, 12, 13, and 14.**

Figure 11: Natriflo HD-Q dynamic binding capacity of BSA versus solution conductivity

NatriFlo HD-Q significantly outperforms competitive membrane adsorbers and reference resin at low conductivity, and meets or exceeds their performance at high conductivity.

dBC BSA @ 10% BT @ 5MV/min for Natrix Recon

HiTrap results were generated with the same buffers and protein (equilibration and sample: 0.1 M Tris pH 8.2, conductivity adjusted with NaCl) using the recommended operating conditions for the column (1 CV/min)

STIC and Sartobind data are extracted from Sartorius's application note in Nature Methods, 2010 (Reference: Sartobind STIC® salt-tolerant membrane chromatography, Fischer-Frühholz et al., Application Note in Nature Methods, 7 December 2010)

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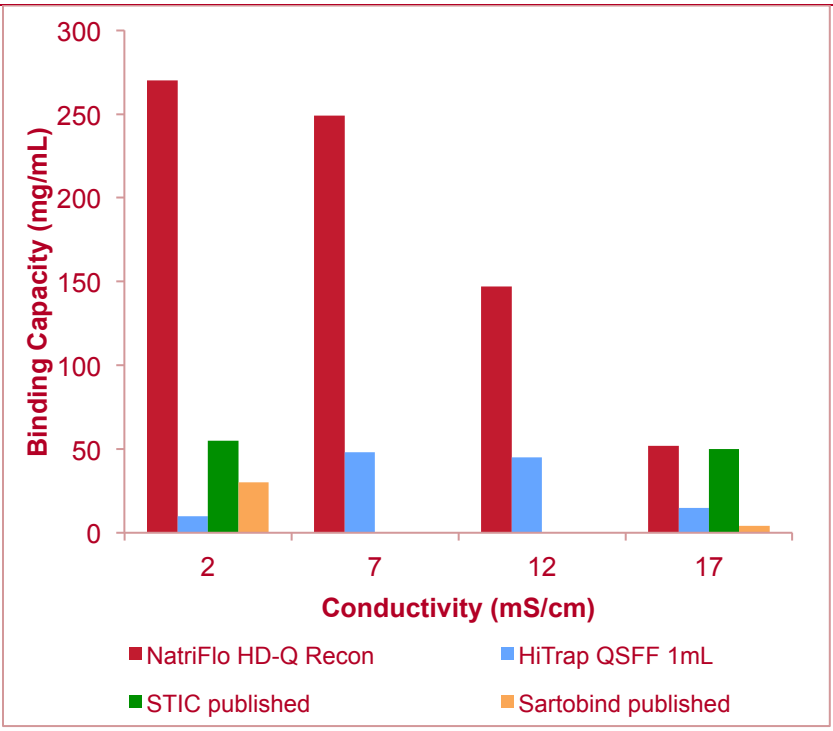


Figure 12 compares the HCP removal capability of NatriFlo HD-Q membrane adsorber with a competitor Q resin and membrane adsorber at two different conductivities. There was a significant increase in HCP concentration for both competitive resin and membrane adsorber-treated solutions when conductivity was increased from 3.8 to 7.5 mS/cm in comparison to NatriFlo HD-Q membrane adsorber.

Figure 12: Effect of conductivity on HCP clearance

NatriFlo HD-Q exhibits excellent tolerance to changes in conductivity when compared to membranes and QSFF resin.

Trial at collaborator.

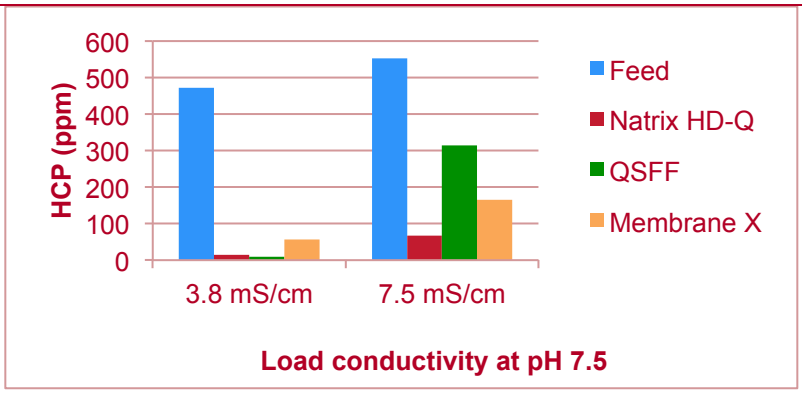
HCP reduction performance for a load @ 1kg/L.

NatriFlo HD-Q can tolerate the increase in conductivity, while QSFF and the other membrane cannot.

Recon @ 10MV/min.

Equilibration buffer: 25 mM Tris-HCl

pH 7.5. Conductivity adjusted with NaCl



NatriFlo HD-Q membrane adsorber demonstrated >4 LRV for endotoxin loads as high as 9 million EU/mL of membrane at both 5 and 15 mS/cm conductivity .

Figure 13. Effect of conductivity on endotoxin clearance

NatriFlo HD-Q achieves >4 LRV for endotoxin loads as high as 9 million EU/mL across a wide conductivity range.

Device: NatriFlo HD-Q Recon

Flow rate: 25 MV/min

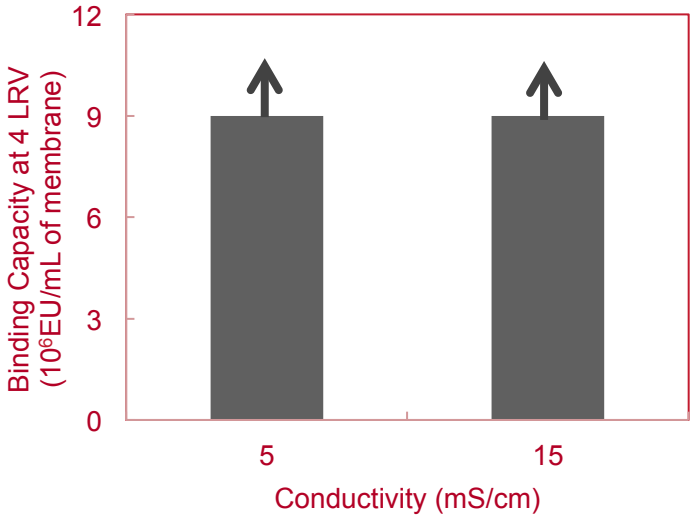
Equilibration buffer: 25 mM Tris + NaCl

pH 8 & 5 mS/cm

Sample: equilibration buffer spiked with endotoxin at concentration > 1000 EU/mL.

Binding capacity was in excess of 9 million EU/mL at 4 LRV irrespective of conductivity in the range of 5 to 15 mS/cm.

(↑ *Performance chart reflects limit of detection)*



Natrix HD-Q membrane also removed MMV virus with >4 LRV at 10 kg/L load from feed having conductivity as high as 10 mS/cm. At 5 mS/cm conductivity, MMV clearance remained constant at 4.8 LRV between 3 to 10 kg/L load (see viral clearance section).

No xMuLV breakthrough was detected at 10 kg/L load from feed having conductivity as high as 15 mS/cm.

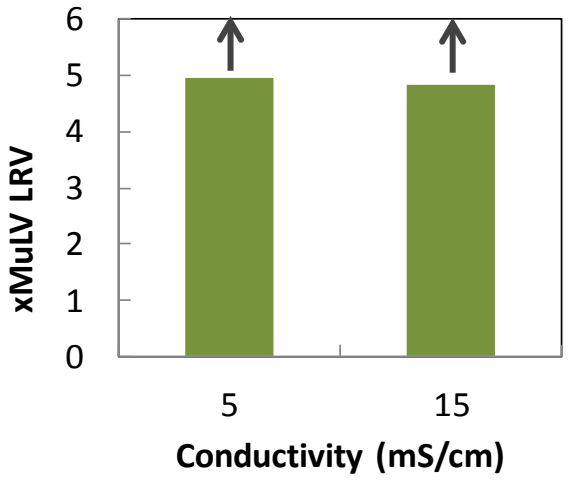
Figure 14. Effect of conductivity on xMuLV clearance
NatriFlo HD-Q maintains xMuLV clearance across a wide conductivity range.

No xMuLV breakthrough was detected in flow-through product for load capacity as high as 10 kg/L;

Feed - 15 g/L mAb at pH 7.5

Flow rate – 10 MV/min.

(↑ *Performance chart reflects limit of detection)*



Phosphate buffer compatibility

Phosphate buffer is widely used in biomolecule purification and especially for Protein A chromatography because of its strong buffering capacity at low concentration, its non-toxicity and the physiological buffering pH range around its pK2 (6.2 to 8.2). However, after elution the presence of phosphate ions typically decrease the performance of anion exchange chromatography operations due to their adsorption tendency to the positively-charged media, leading to reduced binding capacity of process stream impurities.

Thanks to its superior binding capacity Natrix HD-Q membrane is minimally impacted by concentrations of phosphate as high as 50 mM in the process stream.

In collaborator trials, NatriFlo HD-Q membrane adsorbers demonstrated superior HCP clearance in 20 mM phosphate + 100 mM NaCl compared to a competitor salt tolerant membrane adsorber for loads as high as 6 kg/L, providing increased flexibility in operations and process design.

During the same trial, NatriFlo HD-Q adsorbers have also demonstrated much higher loading than their resin competitor (0.12 kg/L) for the same targeted HCP clearance, consequently increasing the unit operation throughput by an order of magnitude.

Figure 15. Presence of phosphate
NatriFlo HD-Q maintains good HCP reduction in presence of phosphate.

Trial at collaborator (Courtesy of Gallus BioPharmaceuticals)

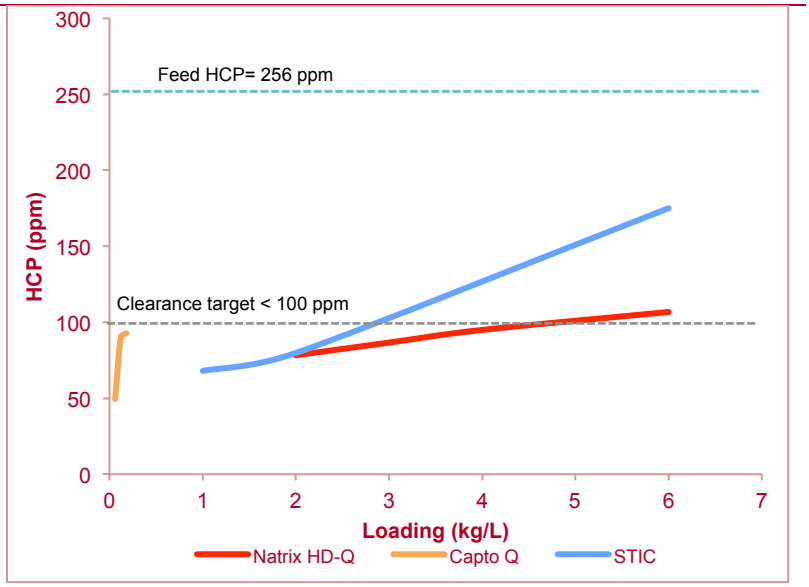
HCP reduction for a load @ 6kg/L and targeted HCP reduction to 100 ppm in presence of 20 mM phosphate and 100 mM NaCl.

Feed HCP= 256 ppm.

NatriFlo HD-Q can perform in the presence of phosphate and still achieve target HCP clearance up to 4.5 kg/L.

Capto Q achieved similar clearance but at much lower load (0.12kg/L).

STIC® did not match Natrix performance after 2kg/L load (STIC is a trademark of Sartorius Stedim Biotech). Capto is a trademark of GE Healthcare Life Sciences.



pH Tolerance

The performance of anion exchange for binding impurities can vary depending on the pH used for chromatography and the available/accessible functional groups for binding molecules with pI values close to the running pH of the system. **Figure 16** shows collaborator data comparing the effect of pH on HCP clearance for anion-exchange media. The NatriFlo HD-Q membrane adsorber gave better HCP reduction with less sensitivity against pH variation in comparison to competitive chromatographic resin and salt-tolerant membranes. Overall, the NatriFlo HD-Q membrane adsorber gave better performance in HCP reduction compared to a competitive salt-tolerant membrane.

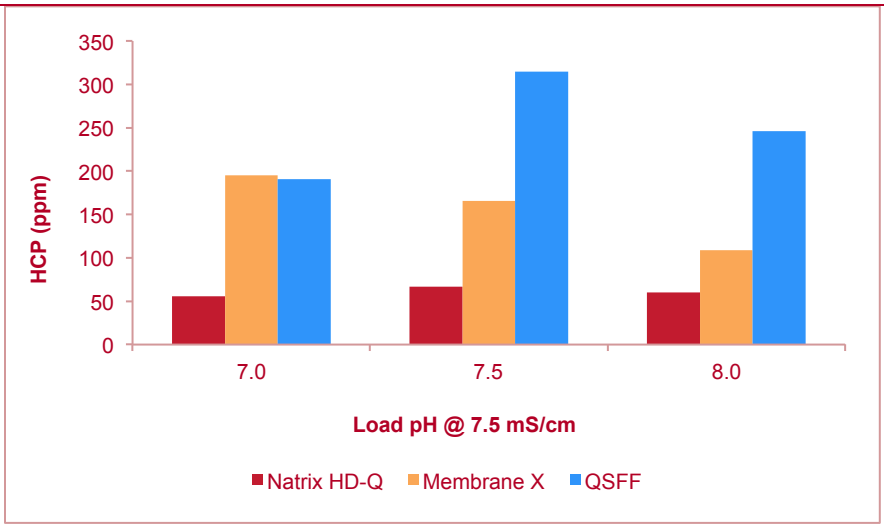
Figure 16: Effect of pH on HCP Clearance

NatriFlo HD-Q achieves consistent and superior HCP reduction over a range of pH conditions compared to QSFF resin and competitor membrane.

Trial at collaborator: HCP reduction performance for a load @ 1kg/L.

3 pH conditions at fixed conductivity show consistent performance for NatriFlo HD-Q, but not for other membranes.

Recon @ 10MV/min. 25 mM Tris pH 7.0, 7.5, 8.0 and fixed conductivity adjusted with NaCl.



Scalability

The excellent performance of Natrix HD-Q membrane adsorbers can be consistently achieved across a range of process scales. **Figure 17 and 18** show collaborator data on the scalable performance of NatriFlo HD-Q for two different mAb process feedstreams, demonstrating consistent HCP and DNA clearance from Recon to Process scale. **Figure 19** shows excellent HCP clearance (> 1 LRV) at both Recon and Pilot scale from a process feed that features a relatively high amount of HCP.

Figure 17: Scalable HCP reduction for a load @ 3kg/L

NatriFlo HD-Q achieves consistent HCP performance at all scales up to 3 kg/L load.

Trial at collaborator (Courtesy of Gallus BioPharmaceuticals)

The level of HCP measured corresponds to the non-binding impurities (pI close to or above the mAb pI).

NatriFlo HD-Q demonstrated very efficient and comparable clearance at all scales.

Equilibration Buffer: 20mM

Phosphate with 100mM NaCl,

pH 7.0

Flow rate 10MV/min

Natrix Products: Recon (0.8 mL), Pilot (15 mL) and Process (115 mL).

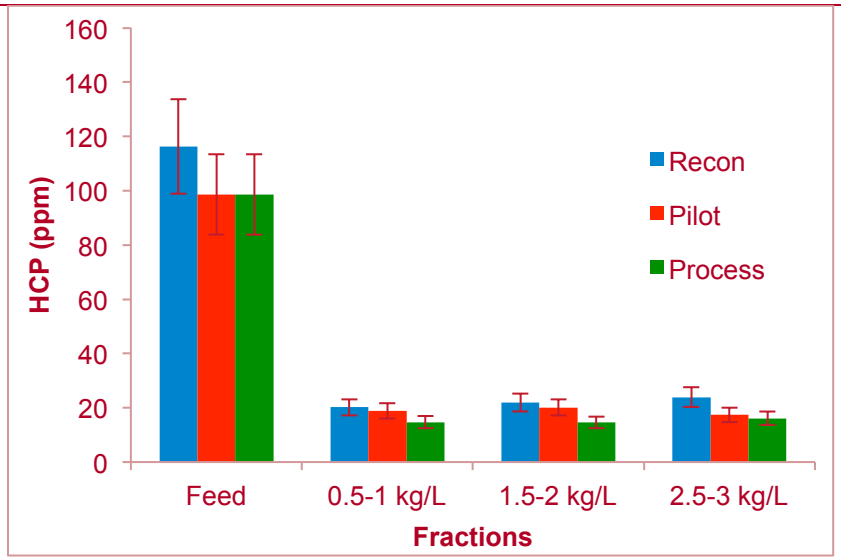


Figure 18: Scalable DNA reduction for a load @ 3kg/L

NatriFlo HD-Q achieves consistent, superior DNA removal (>2.8 LRV) across all scales for a load at 3 kg/L.

Trial at collaborator (Courtesy of Gallus BioPharmaceuticals)

NatriFlo HD-Q demonstrated very efficient clearance at all scales (> 2.8 LRV).

Equilibration Buffer: 20mM Phosphate with 100mM NaCl

pH: 7.0

Flow rate 10MV/min

Recon, Pilot and Process.

(↑ Performance chart reflects limit of detection)

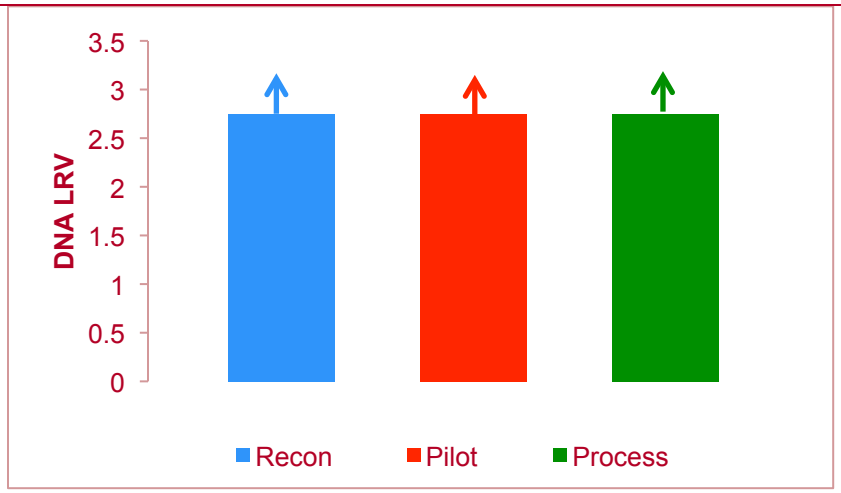


Figure 19: Scalable HCP reduction for a load @ 1kg/L

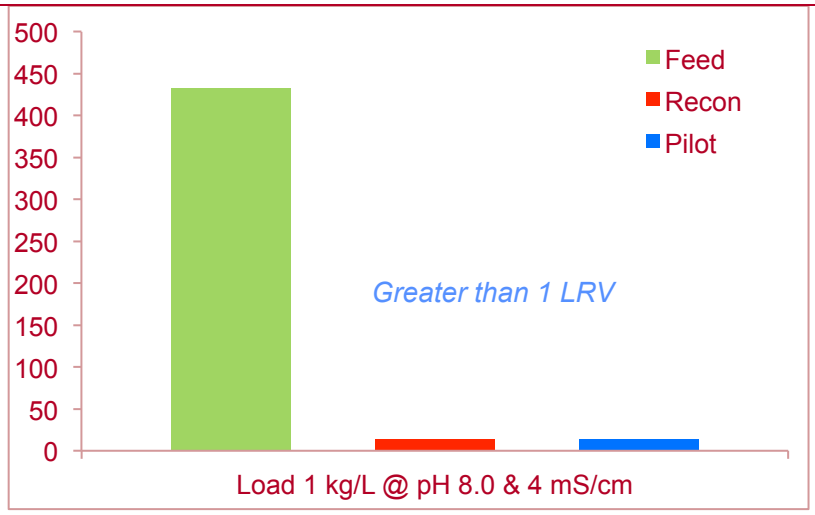
NatriFlo HD-Q achieves comparable HCP performance across two different adsorber scales (0.8 mL, 15 mL).

Trial at collaborator:
NatriFlo HD-Q showed comparable or better reduction of HCP as compared to other membranes (not shown).

NatriFlo HD-Q showed good scalability from lab to pilot and process scale at 1kg/L load.

25 mM Tris-HCl

pH: 8.0



Quality Assurance and Product Validation

NatriFlo HD-Q adsorbers have been developed, manufactured, packaged and distributed under the strictest controls to ensure product quality, safety and consistency. Natrix Separations Inc. operates in accordance with a Quality Management System that is certified compliant with ISO 9001-2008. Manufacturing of Pilot and Process units is carried out in a cleanroom facility that meets or exceeds FDA Good Manufacturing Practice standards through voluntary compliance.

Membranes are tested for flow rate, dynamic binding capacity, mass gain on binding, and dry thickness and mass.

Finished adsorbers are tested for flow rate and dynamic binding capacity. In order to assure consistent and reliable performance, every Pilot and Process unit is also integrity tested, which allows detection of membrane or device seal defects, and verifies compliance with established quality and design specifications. Each batch is tested for endotoxin; an aqueous extract of an assembled adsorber contains less than 0.125 EU/ml as determined by the Limulus amebocyte lysate test.

All materials used in the construction of NatriFlo products have been thoroughly tested and meet the requirements of the current United States Pharmacopeia (USP) monograph <88> Biological Reactivity Tests in vivo for Plastics Class VI. The adsorber housing material is cited for food contact use under the Code of Federal Regulations Title 21, and is non-cytotoxic and non-pyrogenic in accordance with current USP cytotoxicity and pyrogenicity tests. In addition, the Natrix HD-Q membrane has been tested according to Parts 5, 10 and 11 of ISO 10993 and found to be non-cytotoxic, non-sensitizing and non-pyrogenic. Adsorber testing indicates that released particulate matter is well below the requirements for Large Volume Injections in accordance with USP monograph <788> Particulate Matter In Injections.

Real-time and accelerated shelf-life studies are ongoing. The membrane has been demonstrated to have a minimum usable life of 4 years and that of the adsorber unit is expected to be at least 5 years.

Validation guides (Regulatory Support Documents) are available to customers on request.

Ordering Information

Product Code	Product Name	Nominal Membrane Volume (ml of Media)	Units Per Box
NXF-01	Recon Mini	0.2	10
NXF-02	Recon	0.8	5
NXF-10	Pilot	15	1
NXF-20	Process 150	115	1
NXF-50	Process 600	460	1

SALES & TECHNICAL INQUIRIES: Contact Natrix Separations +1 905-319-2682 info@natrixseparations.com