

Disposable Open Platform Approach to Biopharmaceutical Purification

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Introduction

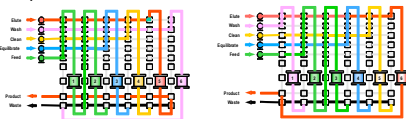
Tarpon Biosystems' BioSMB™ (Biopharmaceutical Simulated Moving Bed) technology is designed to bring the well-documented efficiency and cost savings of Simulated Moving Bed separations to bioprocess. Simulated Moving Bed (SMB) chromatography has been used for decades as a solution to the ton scale purification challenges faced by the food and chemical industries. However, until now issues with sanitary operation and batch control have limited the adoption of SMB in bioprocess. Tarpon's BioSMB technology employs patented disposable technology to make SMB practical for bioprocess. BioSMB systems offer improvements in productivity, more flexible manufacturing configurations, decreases in manufacturing facility footprint and buffer tank requirements, as well as overall cost savings.

Principle of SMB with Disposables



The core principle behind SMB is that in a conventional packed bed column only a small portion of the bed – the mass transfer zone – is actually performing a separation. By breaking the single bed into multiple packed beds, the loading zone can be isolated.

Once an individual bed is fully saturated, it is removed and washed, eluted and regenerated in isolation before being put back into the loading zone. SMB is implemented using a valve system, with all process streams flowing continuously and the packed beds' inlets and outlets switched through the process. Many systems use rotary, multi-port valves, but these are very difficult to adapt to sanitary operation. BioSMB technology uses a set of individually controlled sanitary valves, which has an additional advantage of enabling asynchronous switching between steps.



Tarpon Biosystems' BioSMB systems implement SMB technology using disposable components including a patented and sanitary, single use valve and column system. The BioSMB approach makes single use format chromatography economically advantageous, while the principles of sanitary, cleanable and disposable design enable its use in validated biopharmaceutical production.

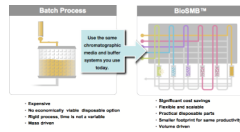
The Valve Cassette is the core of BioSMB technology. It is made of a monolithic polymer and contains all of the system valve seats and fluid interconnections allowing for sanitary single use operation. The Valve Cassette is designed to have no 'dead legs' or places that are difficult to clean. It also has near zero dead volume in the valve seats, thereby minimizing the hold-up volume in the entire flow path.



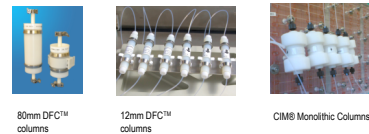
Patented, integrated 16 column position BioSMB™ Valve Cassette. An elasticized diaphragm on one surface of the cassette forms a sanitary seal against a fixed actuator block.

Open Platform for Downstream Processing

BioSMB technology enables the use of all separations technology including packed bed chromatography, membrane chromatography, monoliths, and EBA (expanded bed) chromatography. BioSMB products are designed for bind and elute, size exclusion, flow through ion exchange, and hydrophobic interaction chromatography applications.



Pre-packed, Disposable Format Chromatography (DFC™) columns are used in all BioSMB systems and are completely biocompatible and designed for sanitary operation. The DFC columns can be packed with virtually any commercially available bioprocess media.



Scale-up and Process Continuity

BioSMB technology provides direct and predictable scalability from the lab bench to clinical and full commercial scale. The same disposable, integrated valve array, which can service up to 16 columns or devices without adding significant complexity to the system, is used in all BioSMB systems.



BioSMB Process Development (PD) System - the BioSMB PC-controlled laboratory instrument
BioSMB Production System - PLC-controlled BioSMB system designed for full GMP production

Product/Feature	BioSMB Process Development System	BioSMB Production System
Valve cassette	1 mm Standard (3 mm optional)	3 mm Standard (6 mm, 9 mm options in custom systems)
Ideal Volume range	1-100 L	10 L- 1600 L (3 mm valve) Up to 20,000L with larger valves
Column diameters	12 or 25 mm diameters	50, 80 or 200 mm diameters
Level of compliance	Laboratory product	GAMP 5, CFR part 11 compliant

Technology Applications

Tarpon has successfully demonstrated the value and utility of BioSMB systems in several on-site customer programs in a variety of technical applications including monoclonal antibody, vaccine, and membrane adsorber separations.

Study 1 - MAb Purification in Clinical Manufacturing

In clinical manufacturing, BioSMB systems use less media and less buffers to process the equivalent amount of material and specific productivity at a significantly reduced cost.

	Current Technology	BioSMB™
Column Volume	71 L	2.5 L
No. of columns	1	8
Cycles per Batch	5	88
Dimensions	60 X 25 cm	8 X 6 cm
Column Costs	\$ 121M	\$ 60K
Total Hardware *	\$1.77 M	\$52K

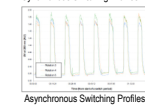
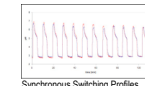
Bioreactor Volume: 2000 L

Expression Level: 5 gm/L

Media: MabSelect SURE

Process Time: 48 hrs for Protein A capture step

Columns: 80 mm diameter x 60 mm height; Pre-packed in OPUSTM format



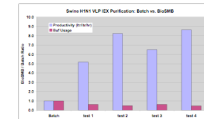
Study 2 – VLP Purification

In a recent study, BioSMB technology was evaluated in a two step purification process (IEX and SEC) in which BioSMB accomplished a fully disposable process while achieving increased specific productivity and decreased buffer consumption.

Swine H1N1 VLP Purification

IEX: 4 tests varying on load amount, flow rate, and others

SEC: 8 tests varying load and product pooling strategy



In IEX separations, specific productivity of BioSMB systems for swine H1N1 was 8x higher than that of batch and buffer consumption is 60% lower. Product impurities and yields were similar. In SEC separations, specific productivity (L/L/hr) of the BioSMB process was 14x higher than batch and product impurities and yields were similar.

Commercial Manufacturing Scenario

BioSMB technology can provide a fully disposable downstream purification process while providing a cost effective and rapid large scale purification process for VLP vaccines.

For 1000L upstream run:

	Columns	Batch	BioSMB™
IEX	100L column	12 (8 X 12 cm)	7L media, 14 cycles/ batch
SEC	90L column	12 (8 X 8 cm)	4.8L media, 32 cycles/ batch

Study 3 – Membranes Adsorbers in Capture Chromatography

Problems such as low binding capacity, large dead volume, and limited scalability, have limited the application of membrane adsorbers to primarily flow-through chromatography. However, multi-device chromatography enables the practical application of membrane adsorbers in capture mode.

BioSMB Configuration

12 Membrane devices

Equilibration: 2

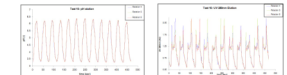
Loading Zone: 4

Wash: 2

Elution: 3

Strip: 1

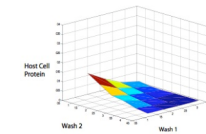
Process cycle time: 5-10 min



	BioSMB™	Batch
Load capacity	Undisclosed	Undisclosed
Recovery	>98%	75%
HCP Reduction	3.5 log	3 log
Specific Productivity *	Undisclosed	Undisclosed
Buffer consumption	55%	100%

Quality By Design

A software model has been developed to enable "in silico" design of BioSMB processes and is designed to run a process simulation as if it were a virtual experiment. It uses the configuration files generated by the method creator for the BioSMB control software and the results are stored in the same format as the BioSMB data produced during a production run or experiment. The data then can be viewed or evaluated for: process optimization; process validation: (a) determining windows of operation without having to explore the entire design space experimentally, (b) balancing process robustness and variability (i.e. in bed packing); process support; and, refining and defining the design space in QbD studies.



Process Simulation Output

Process Economic Model

A process economic model has been created in order to understand the potential impact of BioSMB technology. The economic model describes the savings achieved in converting a batch process to a BioSMB process and the estimated cost savings of consumables, labor, operations, and capital. Model inputs can be customized and adjusted to correctly simulate specific biomanufacturing cost structure, labor rates, operational variables, and a host of other inputs.

Economic Model Output

Breakdown of Cost Savings		per Batch	per Year
Annual Cost Savings	Capital charge	\$ 8,070	193,862
	Consumables	\$ 4,999	-119,983
	Materials	\$ 5,044	121,080
	Labor	\$ 9,217	223,211
		\$ 17,332	418,970
Total Savings		%	23%

NOTE: Cost Savings are for the values of the BioSMB option below that of the Conventional option. Negative values occur where the BioSMB option is more expensive.