The YMC Contichrom® CUBE

A bench top chromatography system for batch and continuous processing
**The Contichrom CUBE System**

**Twin-column flexible bench top system**

The Contichrom CUBE is a flexible modular purification system for process development of biopharmaceuticals such as monoclonal antibodies and pharmaceuticals such as peptides and oligonucleotides.

It enables single-column batch and twin-column counter-current capture (CaptureSMB®) processes, typically used for monoclonal antibody (mAb) purification. The CUBE system can be upgraded for continuous purification of molecules such as peptides and oligonucleotides with MCSGP which automatically recycles side fractions to deliver an all-in-one process tool for challenging purification tasks for all proteins. Additionally the N-Rich process functionality allows the rapid isolation of product-related impurities for CMC development of Biologics.

The systems are offered with pump flow rates of up to 36 mL/min or 100 mL/min.

The unique twin column operational design and software offer several process choices for optimal separation and purification of proteins and oligonucleotides, including batch, integrated batch / sequential polishing and continuous countercurrent processes.

- Run batch, integrated batch and continuous processes with ChromIQ automation software.
- Get 50% more yield with the same target purity and significantly greater throughput.
- Counter-current processes save significantly operating costs, including Protein A resin.
The Contichrom CUBE has extended process capabilities for difficult purification challenges. The system consists of the CUBE hardware and PC with batch mode capability. Process options can include CaptureSMB with AutomAb control, MCSGP, integrated batch / sequential polishing, buffer dilution and N-Rich.

MCSGP is supported by MControl, a dynamic process control function keeping the MCSGP process always at an optimum.

The systems are delivered ready-to-use with fully mounted tubing and pre-delivery IQ/OQ testing.

The CUBE system scales to either the Contichrom TWIN CaptureSMB LPLC (photo right - below) or the Contichrom TWIN MCSGP HPLC (photo left- below).

Both shown are Model 100 of the platform series.
The Contichrom CUBE has batch process capabilities like conventional FPLC systems. Additionally, enhanced continuous process capabilities offer increased performance gains (productivity, yield and throughput).

Twin column capture applications (CaptureSMB / optimized 2C-PCC) and the software tool (AutomAb) are useful for automated optimization of the mAb capture process. Twin column capture processes will result in significant cost-of-goods savings at GMP scale-up.

The Contichrom CUBE Combined adds additional twin-column/membrane process capabilities for polishing applications:

- **MCSP**: Multi-column Counter-current Solvent Gradient Purification. A powerful gradient elution process that increases yield by up to 80% while maintaining target purity. MControl, a dynamic process control tool, keeps the MCSP process at an optimal operating mode.

- **N-Rich**: a process for enriching and isolating minor components from complex mixtures – an ideal tool for fast isolation of product-related impurities for pre-clinical testing.

Flow-2 process is not yet available as a ChromIQ Software wizard.
Powerful Functionalities

- compact benchtop design
- large buffer tray
- clear easy-to-access interface
- high visibility tubing inlets and outlets
- flexible tubing connections
- high performance pumps (36 or 100 mL/min)
- easy-mount clip-in column supports

- 2 long life LED UV detectors each at 280 nm and 300 nm
- easy plug-in CUBE and CUBE+ installation
- pH detector
- 2 conductivity flow cells
- laptop and desktop computer options

Twin columns with column holders
UV (280 & 300 nm) and conductivity
Outlet/column valves
Inlet/column valves
Buffer selection valve
Pressure sensors
Buffer selection valve
Manual purge valves
System/gradient pumps
Drain valve
Drain valve
Gradient pumps
Cooling of product feed and of fractions is important for preserving product integrity. We offer a compact cooling chamber that fits on a lab bench and can accommodate a fraction collector (Foxy R-1), feed bottles and also columns allowing for preparative runs under cooled conditions.

Additional useful accessories include a sample loop system for feed loading, an external valve with an injection loop and a stable, re-usable transport box.
Additional accessories include two external multi-wavelength detectors (190-500 nm), a sample loop system for feed loading, an optional external loading valve with sample injection loops of 500 µL up to 20 mL, a screening valve for column screening addressing up to 6 columns and reusable transport boxes.

- Fraction collectors Foxy R-1 and R-2
- Injection valve system with injection loops of 500 µL up to 20 mL allowing to apply different sample volumes
- Valve system with 6 positions for column screening
- Preparative flow cells in PEEK or steel
- External variable wavelength detector (190-500 nm)
- External variable multi-wavelength detector (190-700 nm)
CaptureSMB (optimized 2C-PCC)

ENABLES
Two-fold faster processing of feed streams preserving product integrity; higher project turnover.

SAVES
30% CAPEX, 30-60% OPEX, 40-60% Protein A consumption, 40-60% buffer consumption.

MCSGP

ENABLES
Isolation of pure components from complex mixtures; 50-90% more yield and higher purity; up to 10x faster processing than batch.

SAVES
Up to 30% CAPEX, 50% OPEX, 70% buffer consumption.

Integrated batch or ‘sequential’ chromatography

The twin-column setup allows to run two consecutive process steps in an integrated way, using in-line dilution between the first and second process step, eliminating intermediate hold steps.

N-Rich

ENABLES
The enrichment of a minor components while simultaneously depleting the large excess of interfering product. It is particularly useful for isolation of product-related impurities.

SAVES
Tedious repetitive analytical separations taking weeks to isolate the compound of interest. With batch processes, up to several hundred analytical injections are needed to isolate sufficient amounts for further characterization. With N-Rich, this can be achieved overnight.
ChromIQ Software

The ChromIQ operating software controls the Contichrom CUBE systems. It supports batch and continuous processes and tools for separation and purification with an intuitive, user-friendly interface.

ChromIQ has easy step-by-step wizards to help you design batch chromatography runs and to convert them to more efficient Contichrom Processes. ChromIQ also includes the AutomAb and MControl dynamic process controllers.

ChromIQ includes a number of features that are particularly helpful for continuous processes such as a buffer management system and cycle overlay display options.

- Drag-and-drop method creation
- Wizards for convenient method creation
- Interactive process picture
- Single-click evaluation
- Easy data export (xlsx, csv, jpg)
- Pre-defined user groups with individual rights management
- Password protected user accounts
- Logging with time stamp and user name
- Electronic signature with checksum of log and measurement files
Load the process wizards from the ChromIQ Software for easy design of processes

**CaptureSMB**

**STEP 1:** Enter feed and column parameters and fit experimental breakthrough curve

**STEP 2:** Define wash, elution and regeneration steps

**STEP 3:** Activate AutomAb control, auto-generate method and receive performance prediction

**MCSGP**

**STEP 1:** Load chromatogram of batch run and select product range and recycling fractions by Drag & Drop

**STEP 2:** Set column size and feed volume

**STEP 3:** Define washing and regeneration steps

**STEP 4:** Activate MControl, set number of cycles and fractionation
AutomAb: dynamic CaptureSMB process control

AutomAb is a tool that automatically optimizes the CaptureSMB process in terms of resin capacity utilization, throughput, and ensuring steady product quality. AutomAb controls the process and maintains optimal process performance effectively offsetting process changes such as feed titer variations and column aging.

Advantages of AutomAb
- works with minimum process knowledge
- runs fully automatically without intervention
- works with low and high feed titers
- works without feed signal measurement
- works with “dirty” feeds with a high impurity signal and low product feed concentrations
- works without detector calibration

MControl: dynamic MCSGP process control

The outcome of chromatographic runs can be influenced by various parameters such as temperature, buffer quality, conductivity, pH and quality of the stationary phase (bed height, resin aging, packing variation) leading to variability. To counteract such effects, we have developed a control algorithm allowing to keep the MCSGP runs always at an optimum by compensating for variations. The resulting MCSGP process is very robust and will run at an optimum without sacrificing productivity.

Advantages of MControl
- MControl compensates for peak shifts by adjusting the fractionation start
- Always the same product in same fraction
- Always the same product quality
- Perfect control of cyclic continuous processes
## Technical Specifications

### Contichrom CUBE systems

<table>
<thead>
<tr>
<th>Feature</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Process capabilities:</strong></td>
<td>Batch (isocratic, gradient), integrated batch, CaptureSMB, MCSGP, N-Rich, Flow-2</td>
</tr>
<tr>
<td><strong>Operating software:</strong></td>
<td>User-friendly operating software with step-by-step wizards to help you to design batch chromatography runs and to convert them into more efficient Contichrom processes, such as MCSGP and N-Rich. ChromIQ also includes dynamic process controllers AutomAb and MControl.</td>
</tr>
<tr>
<td><strong>Software compliance:</strong></td>
<td>ChromIQ software with essential elements of 21CFR Part 11 compliance:</td>
</tr>
<tr>
<td></td>
<td>• Pre-defined user groups, administrators, R&amp;D and production users</td>
</tr>
<tr>
<td></td>
<td>• Rights management for individual user groups</td>
</tr>
<tr>
<td></td>
<td>• User accounts are password protected</td>
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<td></td>
<td>• Logging with time stamp and user name (non-deletable)</td>
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<tr>
<td></td>
<td>• Electronic signature with checksum of log and measurement files</td>
</tr>
<tr>
<td><strong>Pressure rating:</strong></td>
<td>100 bar (10 MPa)/ 1450 psi</td>
</tr>
<tr>
<td><strong>Flow rate range:</strong></td>
<td>• 0.1 – 36 mL/min (Contichrom CUBE 30)</td>
</tr>
<tr>
<td></td>
<td>• 0.1 – 100 mL/min (Contichrom CUBE 100)</td>
</tr>
<tr>
<td><strong>Buffer selection:</strong></td>
<td>16 Inlets (2 x 8-fold buffer selection valve)</td>
</tr>
<tr>
<td></td>
<td>4 Outlets</td>
</tr>
<tr>
<td><strong>UV, fixed wavelength:</strong></td>
<td>2 Long lifetime LED UV detectors, each 280 &amp; 300 nm recording simultaneously</td>
</tr>
<tr>
<td><strong>Conductivity monitoring:</strong></td>
<td>2 Conductivity sensors (1-300 mS/cm)</td>
</tr>
<tr>
<td><strong>pH monitoring:</strong></td>
<td>1-14</td>
</tr>
<tr>
<td><strong>Pump type:</strong></td>
<td>High precision double-piston-pumps with active seal wash</td>
</tr>
<tr>
<td></td>
<td>2 Pumps (CUBE), 4 pumps (CUBE Combined)</td>
</tr>
<tr>
<td><strong>Valves:</strong></td>
<td>4 Reliable multi-position valves</td>
</tr>
<tr>
<td></td>
<td>1 Automated drain valve (CUBE), 2 automated drain valves (CUBE combined)</td>
</tr>
<tr>
<td><strong>Computer hardware:</strong></td>
<td>Stand-alone laptop computer (Windows, 64 bit, full HD resolution, 1920 x 1080 or higher) with ChromIQ software</td>
</tr>
<tr>
<td><strong>Other:</strong></td>
<td>Cold room compatible</td>
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<tr>
<td></td>
<td>Large buffer tray</td>
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<tr>
<td></td>
<td>Portable &amp; compact</td>
</tr>
<tr>
<td></td>
<td>Runs resins and membrane stationary phases</td>
</tr>
<tr>
<td><strong>Dimensions:</strong></td>
<td>CUBE module 1: 450 mm x 509 mm x 370 mm (20.0” x 17.7” x 14.6”)</td>
</tr>
<tr>
<td></td>
<td>CUBE module 2: 450 mm x 509 mm x 214 mm (20.0” x 17.7” x 8.43”)</td>
</tr>
<tr>
<td></td>
<td>The modules are stackable</td>
</tr>
<tr>
<td><strong>Weight:</strong></td>
<td>CUBE module 1 &amp; 2: 17 kg (38 lb)</td>
</tr>
<tr>
<td><strong>Materials:</strong></td>
<td>All biocompatible</td>
</tr>
<tr>
<td></td>
<td>High pressure side capillaries: PEEK</td>
</tr>
<tr>
<td></td>
<td>Low pressure side tubing: PTFE</td>
</tr>
<tr>
<td></td>
<td>Fittings: PEEK</td>
</tr>
</tbody>
</table>
GMP Scale-Up

Twin-column process scale

Contichrom® TWIN platform: Best-in-class GMP skids

Contichrom TWIN CaptureSMB 1000 custom unit shown above.

Example TWIN LPLC product features:
• Ability to run batch, integrated / sequential batch, parallel batch and (continuous) CaptureSMB.
• CIP Option
• Scale-up method conversion
• Allan-Bradley Rockwell or Delta-V operating system
• Compliant with ASME/BPE, GAMP, ASTM, 21CFR part 11
• Integrated Buffer In-line Dilution (BID)
• Flow accuracy: better than 0.5% variation.
• Gradient accuracy: better than 0.5% variation
• Pressure rating: 7.5 bar (108 psi)
• Flow path: 316L stainless steel
• Optional single use interface (shown)

Reference papers: Bristol Myers Squibb using Contichrom Twin GMP scale-up system and performing process simulation and process validation:


<table>
<thead>
<tr>
<th>TWIN CaptureSMB LPLC</th>
<th>Min L/min</th>
<th>Max L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twin 100</td>
<td>0.004</td>
<td>0.8</td>
</tr>
<tr>
<td>Twin 300</td>
<td>0.02</td>
<td>3.3</td>
</tr>
<tr>
<td>Twin 500</td>
<td>0.06</td>
<td>10</td>
</tr>
<tr>
<td>Twin 1000</td>
<td>0.12</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TWIN MCSGP HPLC</th>
<th>System Flow Rate range (L/min)</th>
<th>Flow Rate range (L/min) [Recommended]</th>
<th>Column ID range (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0.0055 - 0.94</td>
<td>0.01 – 0.67</td>
<td>2.5 - 10</td>
</tr>
<tr>
<td>300</td>
<td>0.023 – 3.74</td>
<td>0.03 – 3.33</td>
<td>10 -20</td>
</tr>
<tr>
<td>500</td>
<td>0.063 – 10.7</td>
<td>0.15 – 8.33</td>
<td>20 - 45</td>
</tr>
</tbody>
</table>
Training, Maintenance, and Repair

A reliable and cost-effective service network

Purchasing a CUBE System and operating it is only part of a customer's value proposition. After sales support such as Preventive Maintenance (PM) and total life cycle costs are an important consideration in a system’s procurement evaluation.

We offer PM, repair and system validation and qualification support including IQ-OQ and a generic PQ testing scheme. We also offer an annual Software PM package.

We perform on-site and off-site training, webinar-based product support and we organize annual workshops on continuous chromatographic purification.

Our system is designed to have very low maintenance costs: only wear parts from pumps and valves need to be exchanged occasionally in an easy way without disassembling the system.

We offer continued support through remote control system access allowing to guide the user in using the system beyond the initial training.

We offer comprehensive and cost-effective Preventive Maintenance and Repair Service packages.

Worldwide Preventive Maintenance and Repair Service packages. On-site and off-site service with fast turnaround times.

For details please inquire about a quote at your local YMC ChromaCon representative.
Contact us now to find out how you can solve your separation challenges more easily

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