Case Study: Fractionation of Blood Plasma with Contichrom®
Executive summary

- Contichrom® can simplify the standard plasma fractionation process, resulting in higher yields and lower costs
- The Cohn Process is modified, not substituted with acceptable regulatory consequences
- Access to novel plasma proteins e.g. hyperimmunes
- Higher overall yields up to 30%
- Operational cost reduction estimated up to 2 M€ p.a. compared to batch chromatography
- Capital expenditure reduction up to 30%
- Equipment supplied by partner engineering companies
Blood Plasma

- Plasma contains 55–60% albumin (35-50 g/L)
- Least abundant proteins: Interleukines (ng/L)
- 289 proteins in plasma documented (2005)
- 100 proteins used in diagnostic assays
- ca. 20 plasma protein therapeutics, three proteins account for 80% of revenue
- prices of albumin drop
- many proteins not exploited (2005) (e.g. plasmin, apolipoprotein A1, fibronectin)

Source: John Curling and Christopher Bryant, The plasma fractionation industry, BioProcess International March 2005
Plasma Fractionation: Challenges

- **Large volume**: 22 mio litres of plasma collected p.a.
- **Source**: plasma limited
- **Process**: conventional Cohn fractionation processes operate with low yields
- **Affinity chromatography**: is specific but expensive and the ligand has to be tailored for each protein of interest
- **Batch chromatography**: demands high CAPEX and provides lower yields than affinity chromatography
- **COG**: pressure on margin due to high manufacturing cost and increased cost of virus testing
Key drivers for plasma fractionation

- Optimization of COG
- Access to new technology ensuring improved yields of safe products
- Integration into existing fractionation processes and infrastructure
- The ability to develop novel therapeutics
- Market demand for higher purity products
Contichrom®: Benefits using MCSGP

**ENABLES**
- the large volume purification of chemicals and biologics
- the generation of lifecycle extensions for marketed biologics

**SAVES**
- 30% CAPEX & 50% OPEX
- Purity increase by 50%
- Yield increase by 50%
- Throughput increase 10x
- Buffer reduction -75%

**ACCELERATES**
- Discovery of leads
- Development retaining product profile at upscaling
MCSGP process principle: recycle until it’s pure

Conventional batch chromatography

- Impure product to waste
- More and purer product

ChromaCon’s novel internal recycling chromatography (MCSGP)

- Reprocess impure product
- Cut narrow = obtain purer product
Typical fractionation process (simplified)

- **Frozen plasma**
  - **Cryo precipitate**
    - Chrom.
    - Chrom.
    - Fibrinogen
    - vWF
    - FVII
  - **Cryo-poor plasma**
    - Batch adsorption
    - Chrom.
    - Protein C
    - C1 inhibitor
    - ATIII
    - FIX
    - FVII

- **Ethanol precipitation**
  - Chrom.
  - Albumin
  - IgG

- **Ethanol precipitation**
  - Chrom.
  - AAT
Integration of MCSGP into the Cohn Process

- Replacement of 3 batch chromatography steps and one precipitation step by MCSGP
Estimated unit dimensions (cryo-poor)

- Cryo-poor plasma (3‘500 kg purified product p.a.)

<table>
<thead>
<tr>
<th>Performance overview</th>
<th>batch</th>
<th>MCSGP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Productivity (throughput)</td>
<td>[g/L/hr]</td>
<td>0.9</td>
</tr>
<tr>
<td>Buffer consumption</td>
<td>[L/g]</td>
<td>3</td>
</tr>
</tbody>
</table>

| Buffer consumption per month runtime            | [m3/month] | 863   | 345  |
| Overall volume of stationary phase              | [L]       | 331.8 | 142.5 |

| Units dimensions (no limit on column i.d.)      |       |       |
| Number of columns per unit                      | [-]   | 1     | 4    |
| bed height                                      | [cm]  | 25    | 15   |
| column inner diameter                           | [cm]  | 130   | 55   |

- Conclusion: MCSGP is the superior process option to obtain high purity products for large volumes
Estimated unit dimensions (cryo-precipitate)

- Cryo-precipitate (100 kg purified product p.a.):

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<tr>
<td>Productivity (throughput) [g/L/hr]</td>
<td>1.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Buffer consumption [L/g]</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Buffer consumption per month runtime [m3/month]</td>
<td>38</td>
<td>15</td>
</tr>
<tr>
<td>Overall volume of stationary phase [L]</td>
<td>12.3</td>
<td>3.5</td>
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<th>Units dimensions (no limit on column i.d.)</th>
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<tr>
<td>bed height [cm]</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>column inner diameter [cm]</td>
<td>25</td>
<td>10</td>
</tr>
</tbody>
</table>

- Conclusion: MCSGP provides higher product yields and lower operating costs
OPEX savings with Contichrom® (MCSGP)

- E.g. for cryo-poor plasma

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<th>OPEX reduction by MCSGP</th>
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<tbody>
<tr>
<td>Buffer consumption per month runtime [m3/month]</td>
<td>863</td>
<td>345</td>
<td>-60</td>
</tr>
<tr>
<td>Overall volume of stationary phase [L]</td>
<td>331.8</td>
<td>142.5</td>
<td>-57</td>
</tr>
</tbody>
</table>

- Assuming 0.2 €/L buffer (WFI quality), 1L stationary phase 1‘000 € and 1 year lifetime of stationary phase

- Estimated annual buffer & resin cost: batch=2‘400 k€, MCSGP=970 k€

- Annual buffer/resins savings: 1‘430 k€

- Estimated additional cost savings of 0.5 M€ due to lower labour and maintenance cost

- Annual total savings: up to 2 M€

- Additional COG benefit: up to 50% more product can be isolated at high purity
CAPEX savings

- Due to significantly smaller footprint and utility use, estimated reduction in CAPEX is up to 30% for downstream processing operations (10 M€ for a total budget of 100 M€)

- Detailed unit dimensions and subsequent CAPEX reduction estimate need to be refined in basic engineering phase
Optimized use of Contichrom® equipment

- From the analysis of the process, at least one pilot-scale and one production scale equipment is needed

- The pilot-scale equipment would be used in the cryo-precipitate branch and in a side-branch for the cryo-poor plasma (up to 4 products simultaneously)

- The production scale equipment is the backbone of the cryo-poor plasma after initial processing (3 fractions simultaneously)
Pricing of Contichrom® equipment

- Pilot-scale Contichrom® unit for cryo-precipitate:
  - ≈ 100 kg p.a. purified products, column i.d. ≈ 10cm
  - Delivery time ca. 9 month

- Production scale Contichrom® unit for cryo-poor plasma:
  - ≈ 3‘500 kg p.a. purified products, column i.d. ≈ 55cm
  - Delivery time ca. 12 month
Equipment supplied by partner companies

- ChromaCon works with reputable engineering companies as supplier for the
  - Engineering, automation
  - Construction, installation, validation

- Qualified partner companies with plasma processing plant/equipment experience:
  - NNE Pharmaplan
  - Glatt Engineering
  - M + W Process Industries
  - Bayer Technology Services