



A comparative study of Cohn and chromatographic fractionation using a novel affinity “Cascade Process”.

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Chromatographic fractionation •

Advantages

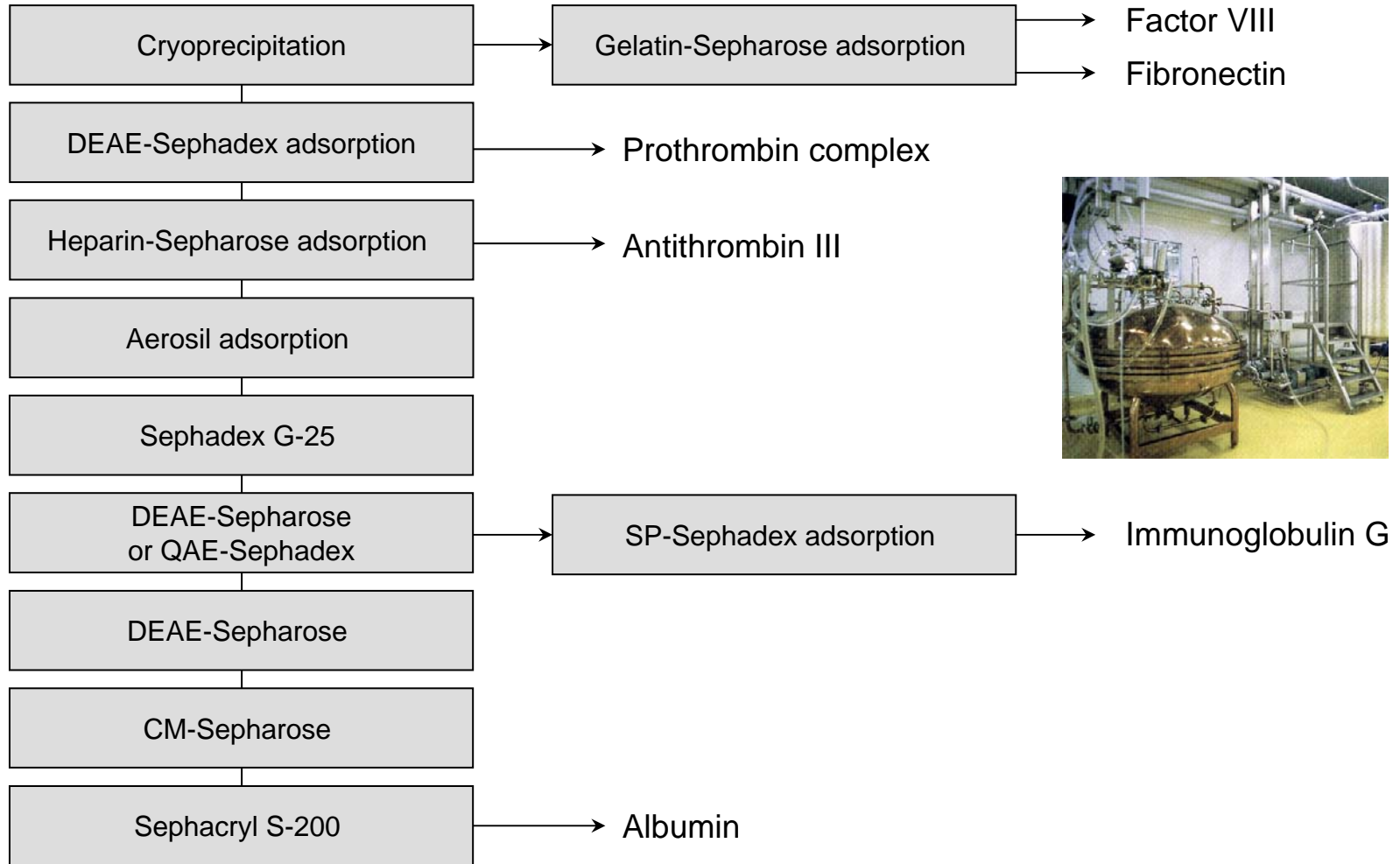
- Accepted downstream methods off Cohn trunk
- Existing processes with chromatographic steps
- Widespread use in biotechnology industry
- Closed system of fractionation/automation
- Controlled environment processing
- Partitioning effects with respect to pathogens
- No use of organic solvents or filter aids
- Allows isolation of many proteins
- Suited to all scales of manufacturing

Disadvantages

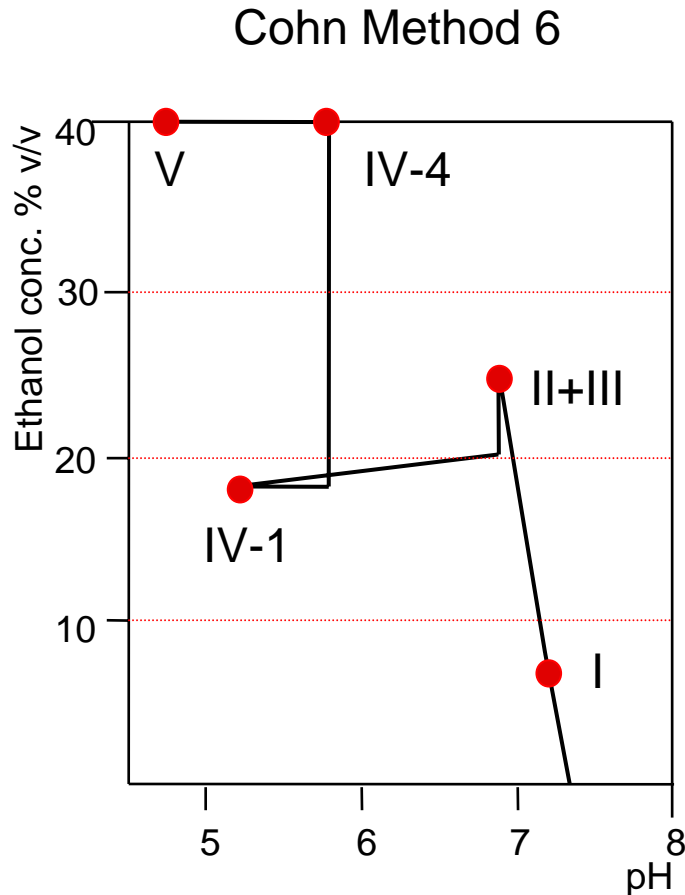
- New products require approval/clinicals
- New products require local registration
- Not in widespread use as trunk scheme
- USP and WFI water consumption
- Buffer salt consumption
- Engineering requirements to handle buffers
- No use of filter aids (pathogen clearance)
- Resin* usage/manufacturer dependent
- Resin capacities/column scalability

* not perceived as disadvantage by biotech industry

Chromatographic fractionation - 1982



Cascade process backbone compared to Cohn



Cascade

Original Plasma

pH 7.24, Cond. 11mS/cm

Buffered Plasma for 1st Column

pH 7.52, Cond. 12mS/cm

Load for 2nd Column

pH 7.57, Cond. 13mS/cm

Load for 3rd Column

pH 7.58, Cond. 15mS/cm

Load for 4th Column

pH 7.6, Cond. 18.5mS/cm

Load for 5th Column

pH 7.6, Cond. 17mS/cm

Load for 6th Column

pH 6.1, Cond. 5mS/cm



Yields of the Cohn process •

Target Protein	Yield Cohn trunk (%)	Yield Cohn branch (%)	Yield Cohn total (%)	Industry average ¹	Industry average ²
Factor VIII by cryoprecipitation	40	45	18	140-270 IU	~200 IU
Factor IX	-	-	-	-	~350 IU
Immunoglobulin G	66	80	53	3-4 g	~3.5 g
Alpha ₁ -protease inhibitor	23	66	15	-	~0.2 g
Albumin	95	90	86	22-28 g	~25 g

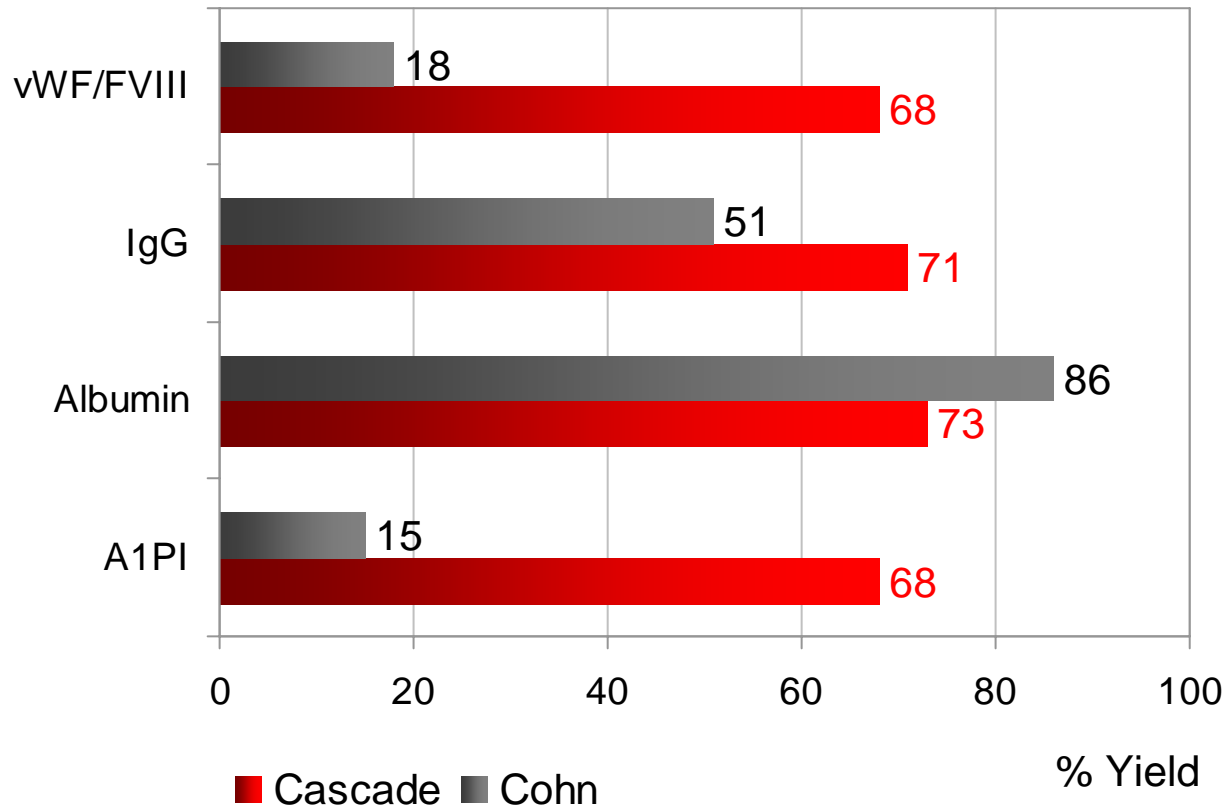
Yield figures in % from industry sources.

1. Industry average from WFH "Contract fractionation"

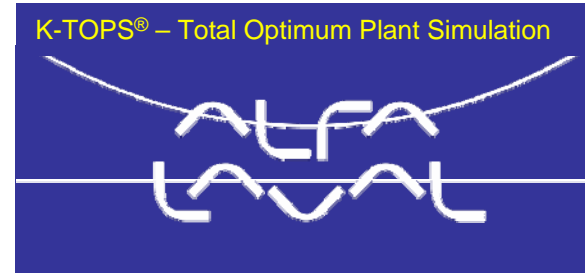
2. Gustafson, M., PPTA: <http://www.fda.gov/cber/summaries.htm#plasma>

Curling, JM, Bryant C., BioProcess International, March 2005.

Yield comparison in model



Engineering study •



- Undertake study to understand economic viability of Cascade Process
- Use worst-case scenario for Cascade Process
- Non-optimised process input from preliminary 4 L scale

- Evaluate Cascade (PPPS) Process for plasma fractionation versus standard Cohn Process

- Evaluation focused upon a 500,000 L Plasma /yr Greenfield facility

- Evaluation to be an “apples-to-apples” comparison between the two processes, utilizing improved technologies/approaches for both facilities

Basis for comparison •

- 4 products produced
 - vWF/Factor VIII
 - IgG
 - Albumin
 - A1PI
- Both facilities are new 2-story facilities
- Cost basis is Northeast USA



- 7 production areas within each facility

- Backbone (Fractionation / PPPS)
- vWF/fVIII Pre-viral (Cohn only)
- IgG Pre-viral
- Albumin Pre-viral
- A1PI Pre-viral
- vWF/fVIII Post-viral
- IgG Post-viral (PPPS only)
- A1PI Post-viral



- Cohn facility processing a batch every 2 days
 - 3,500 L plasma batch
- Cascade facility processing a batch through backbone every day
 - 1,750 L plasma batch
 - Albumin also processes a batch every day
 - All other products within Cascade pool two batches and process every 2 days
- 44 weeks of production = over 500,000 L/year of plasma
- 1.3% product failure rate (2 failed batches/yr)

- 7 day/week, 24 hr/day operation
- 3rd shift operation limited to cleaning and setup when possible
- Ensures operability of facility
 - Limits the number of production operations for a batch within a single day
 - Enables delays in production to be addressed within the later part of the 2nd shift (or 3rd shift if necessary)

- Process Evaluation/Comparison using K-TOPS Plant Simulation
- Key items of evaluation included
 - Batch size
 - Buffer delivery (in-line dilution)
 - Buffer storage
 - Facility configuration (single/multi-story)





- Cascade facility slightly smaller than Cohn facility
(98,000 sq ft for Cascade facility versus 100,000 sq ft for Cohn)
 - Cohn also has an additional 1,000 sq ft external area for outdoor ethanol area
- Cascade footprint 15% smaller than Cohn facility
(49,000 sq ft for Cascade facility versus 56,000 sq ft for Cohn)
- Both facilities are 2-story facilities
- Reduced size of Cascade footprint due to no ethanol within facility

Facility differences •

- Over 10,000 sq ft of Class 1 Div 1 area (ethanol containing) in Cohn facility
- Over 10,000 sq ft of Cold Room area in Cohn facility vs <2,000 sq ft for Cascade
- Fractionation area smaller in Cascade facility (4,600 sq ft vs 8,100 sq ft)
- Buffer area larger in Cascade (10,500 sq ft vs 5,200 sq ft)

Cascade facility breakdown •

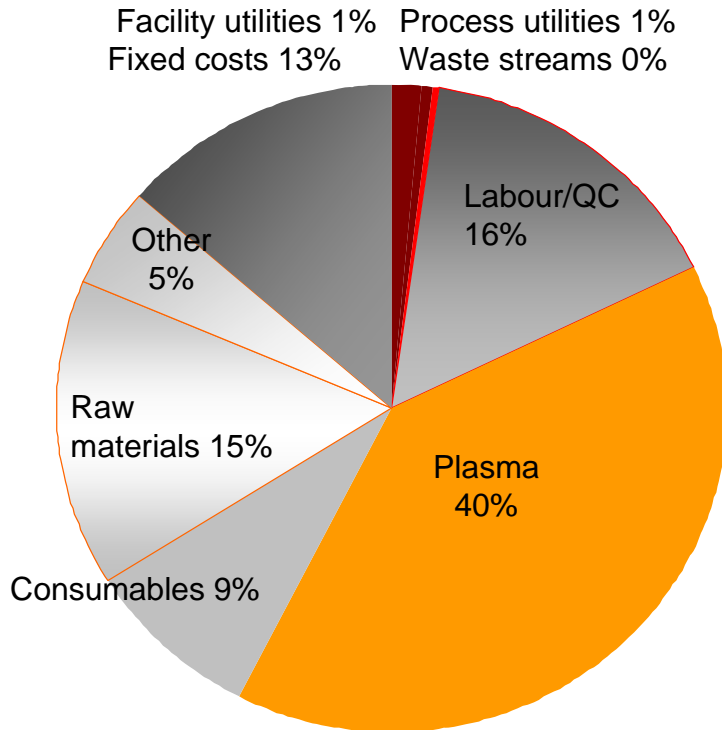
- 3.34 acres of land required
 - ½ acre less than 2-story Cohn facility
- 98,000 sq ft
 - 37,000 sq ft – Class 100 K
 - Ep Ptd GWB - walls/ceiling, TOE Flr., Class 100,000 HVAC
 - 18,000 sq ft – Admin
 - Carpet, acoustical ceiling, painted finishes, Comfort HVAC
 - 43,000 sq ft – Utility
 - Sealed concrete, OTC, minimal finishes, Unclassified Controlled HVAC

Cost type	Definition
Facility utilities	HVAC clean steam, cooling, plant steam, water, power
Process utilities	HVAC clean steam, cooling, plant steam, water, power, USP water, WFI
Waste streams	Process waste
Labour/QC	Direct, supervisory and other labour
Plasma	Source plasma @ US\$ 120/litre*
Consumables	Resins, membranes, filters, bags
Raw materials	Buffer salts
Other	Product failures, royalties, transportation, maintenance (at 6%)
Fixed costs	Depreciation (straight-line, 10 years), overhead (at 5%), local taxes

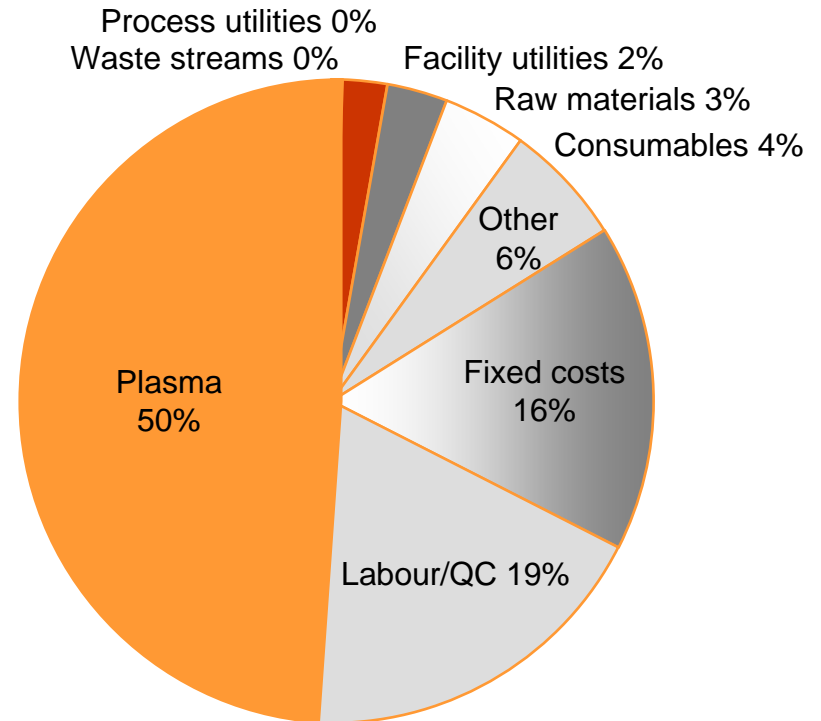
* \$105-\$110/litre IBPN, April 2005 (P. Robert, MRB)

Cost comparison including plasma

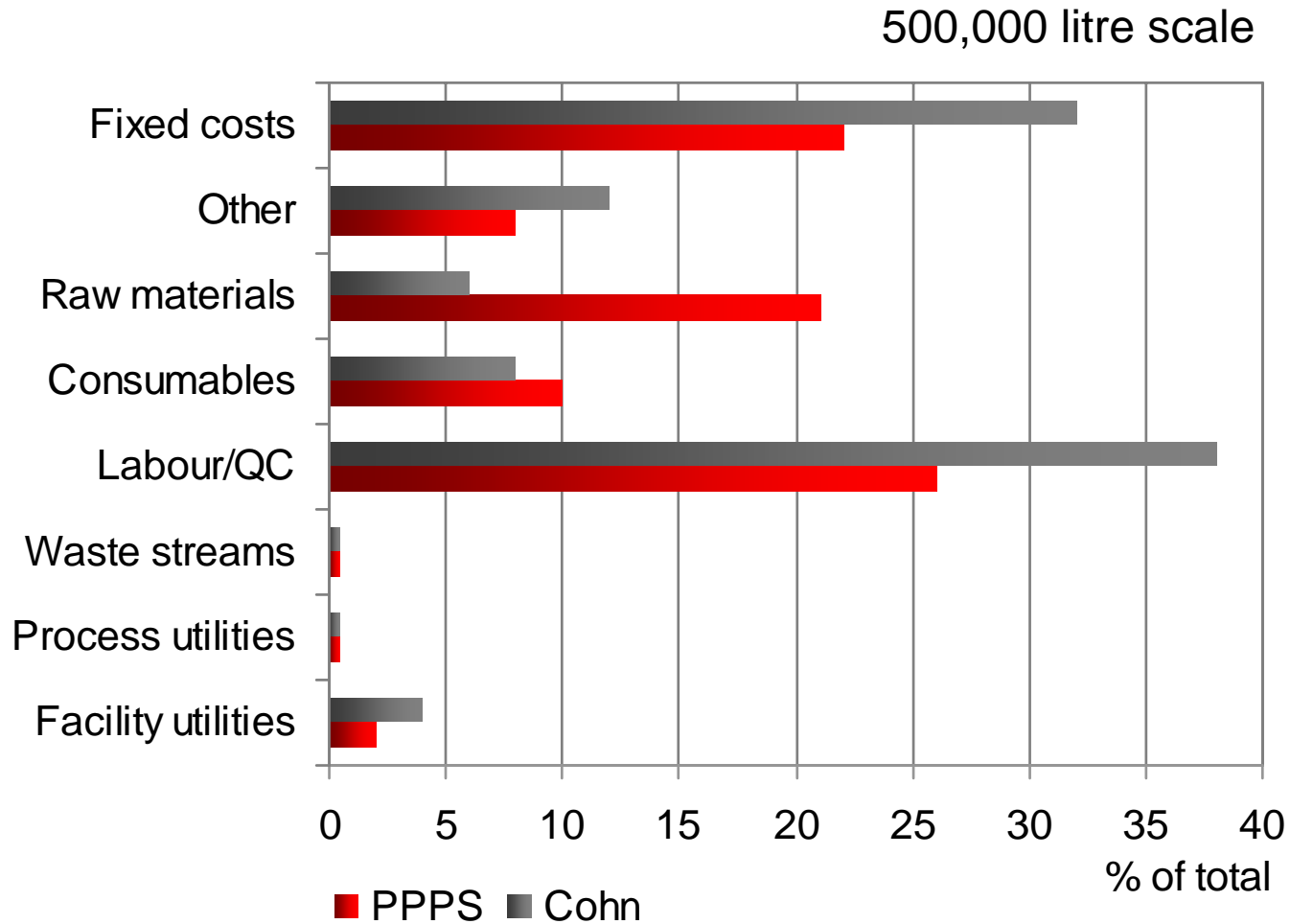
Cascade process (Trunk + downstream)



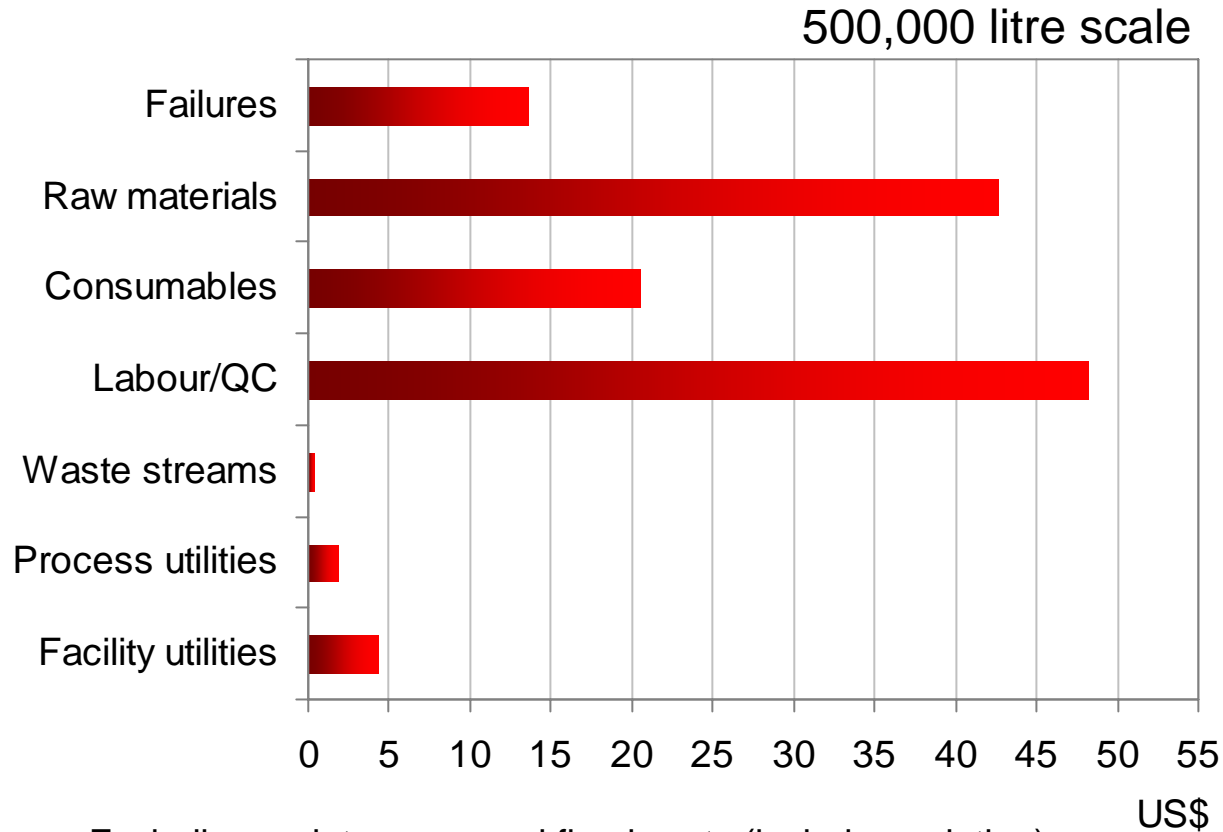
Cohn process



Cost comparison excluding plasma

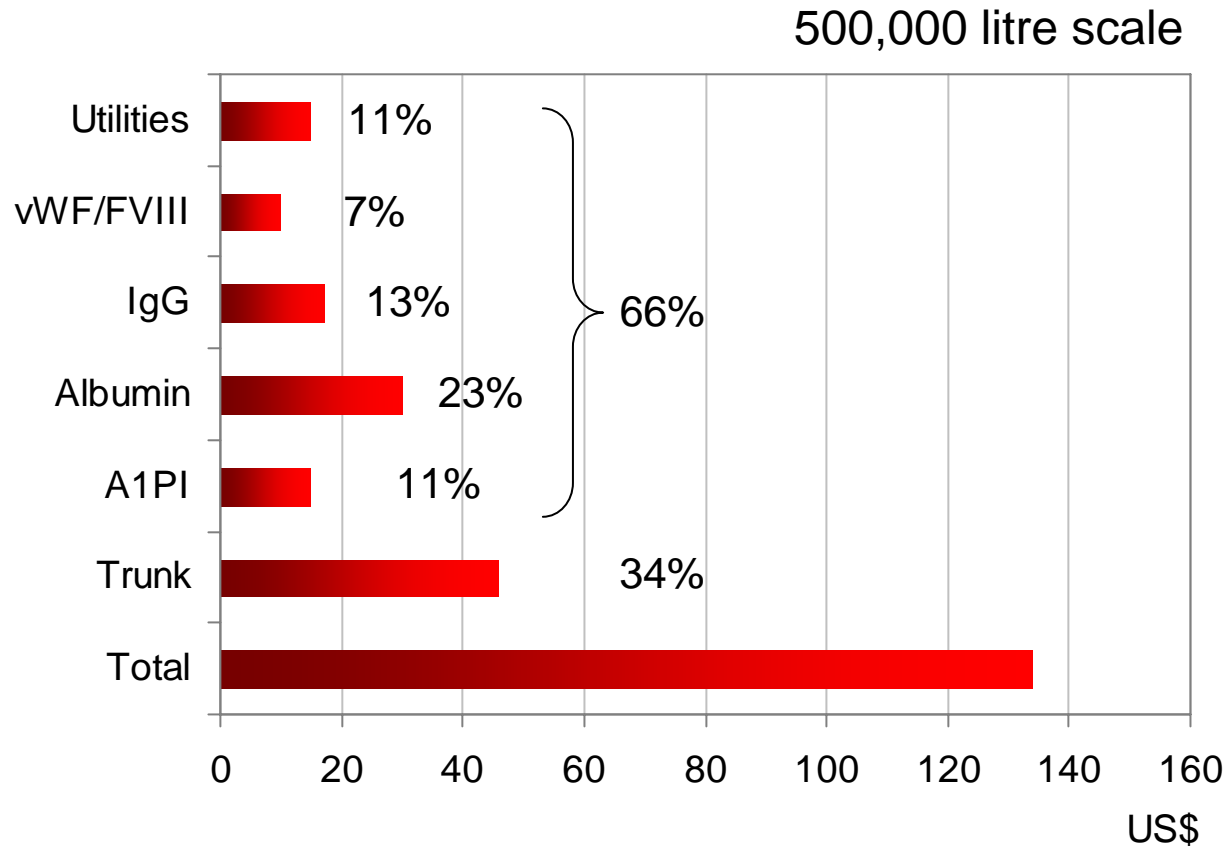


Cascade costs per litre plasma fractionated •



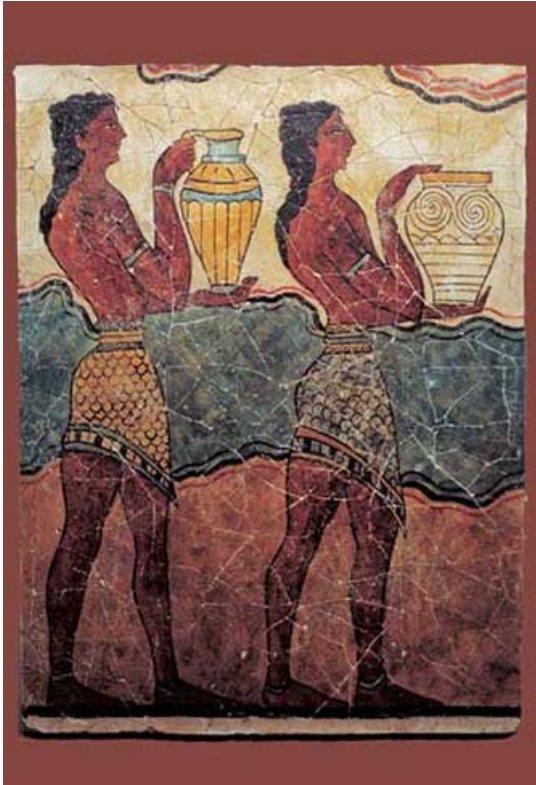
- Excluding maintenance and fixed costs (incl. depreciation)
- Raw materials includes all buffers and sanitisation (CIP) solutions
- Resins (Consumables) calculated at US\$ 500 – \$1,500/litre
- Labour calculated at US\$ 25-40/ man-hour
- **Total processing cost = US\$ 134/litre**

Costs per protein fractionated



- Excluding maintenance and fixed costs (incl. depreciation)
- Non-dedicated costs allocated 20% per protein recovered
- **Total processing cost = US\$ 134/litre**

Operating costs



Bringing vases, Knossos

- Cascade Operating Costs: \$150 MM /yr
- Cohn Operating Costs are \$125 MM /yr
- Key differences in operating cost are in consumables and raw materials

	Cascade	Cohn
Consumables	\$10 MM	\$5 MM
Raw Materials	\$21 MM	\$4 MM

Project costs (500,000 L/yr) •

- Project costs for both Cohn and Cascade are approximately \$129 MM
 - Total direct costs
 - Construction costs
 - Engineering costs
 - Contract administration costs
 - Validation costs
 - Start up and commissioning costs
 - Contingency (13%)



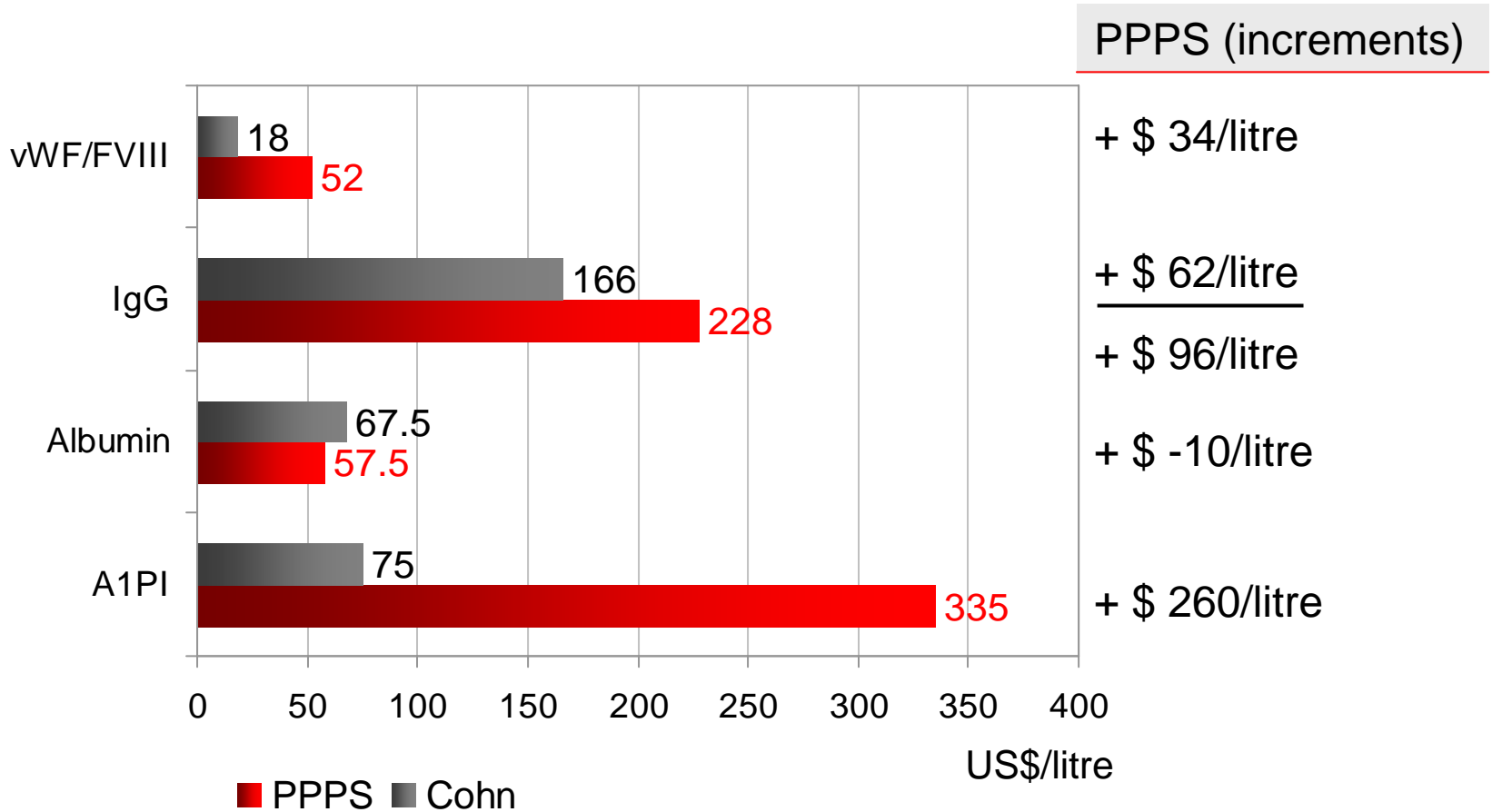
Revenues (US prices, 2004) •

Cascade	vWF/FVIII	IgG	Albumin	A1PI	
Yield	52%	70%	73%	68%	
\$/g	\$10,000	\$38	\$2.25	\$330	
g/batch	18	20,975	89,500	3,552	
\$MM / yr	26.7	117.2	29.6	172.3	
\$ / L plasma	\$52	\$228	\$57.5	\$335	\$672.5

Cohn	vWF/FVIII	IgG	Albumin	A1PI	
Yield	18%	51%	86%	15%	
\$/g	\$10,000	\$38	\$2.25	\$330	
g/batch	6	15,243	105,000	798	
\$MM / yr	9.1	85.1	34.7	38.7	
\$ / L plasma	\$18	\$165.5	\$67.5	\$75	\$326

Batch size = 3,500 litres

Revenue comparison



- PPPS revenue for 500,000 L plasma facility is over 2x the revenue for Cohn
- PPPS revenue is \$341 MM / year (\$140 MM from vWF/FVIII + IgG)
- Cohn revenue is \$165 MM / year (\$92 MM from vWF/FVIII and IgG)



King Minos Throne, Knossos



Steve Burton



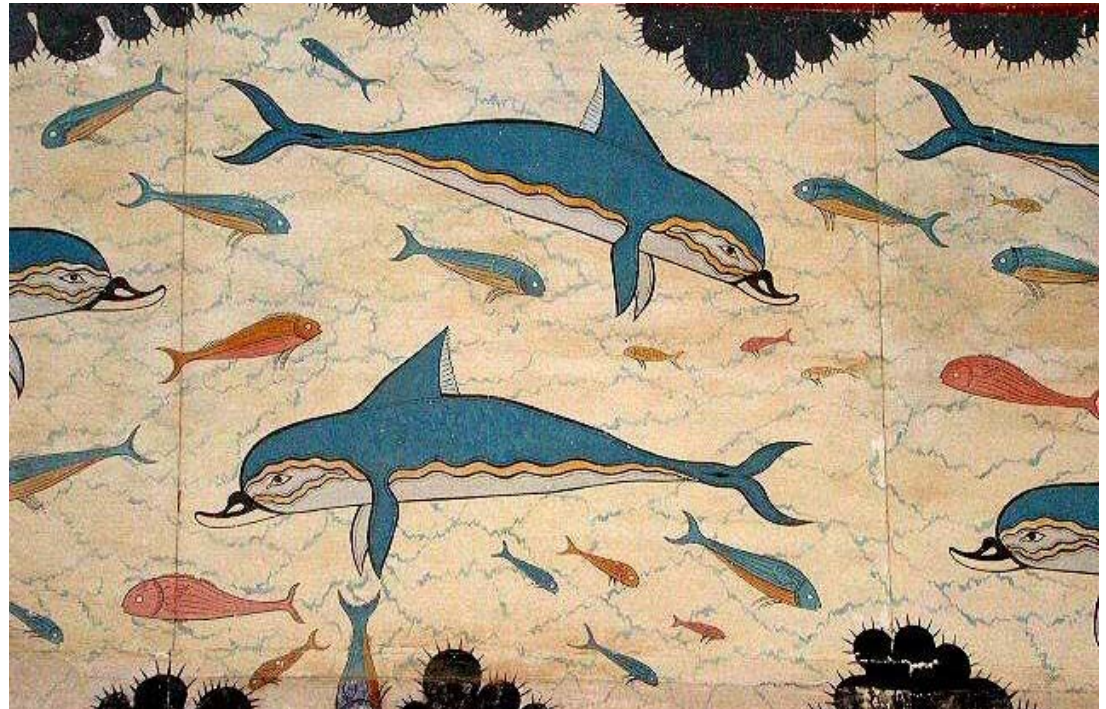
David Hammond



Ruben Carbonell
Patrick Gurgell



James Weiss



Dolphins, Knossos