

The potential for low cost manufacturing of safe plasma products

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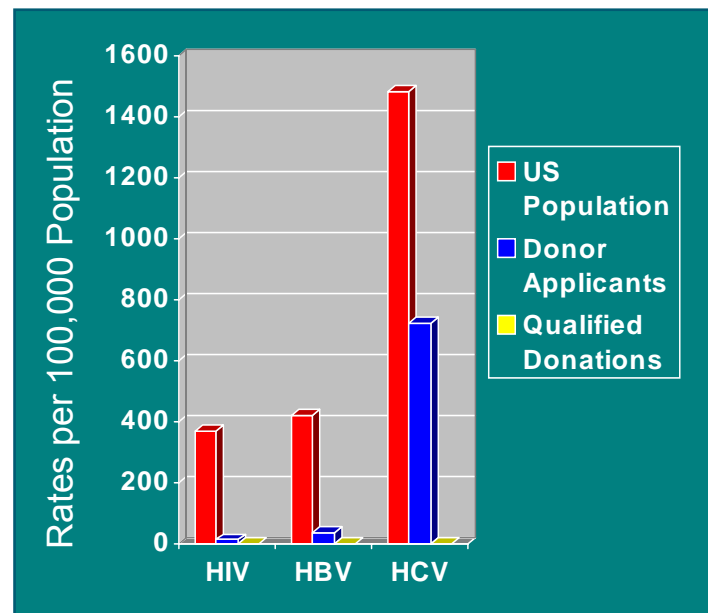
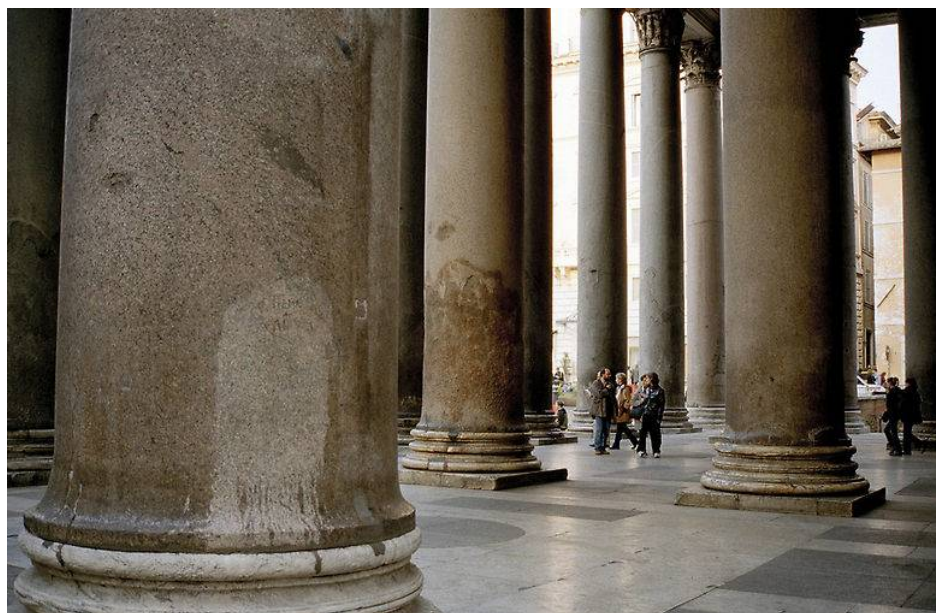
Neil Goss, *Further Options Ltd.*

Andrew Sinclair, Janice Lim, *BioPharm Services Ltd.*

Mahesh Prashad, *Sartorius Stedim Biotech*



Viral safety at the plasma stage



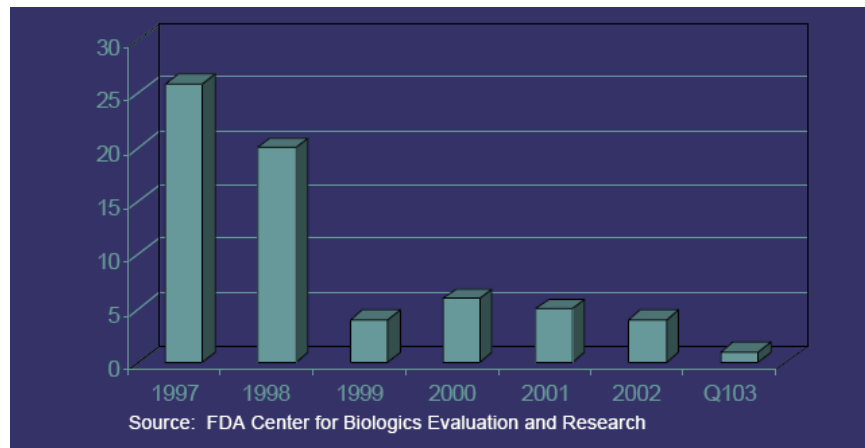
Adapted from Kreil, T, IPPC 2004

- 100 fold reduction of risk by selection
- 100,000,000 fold reduction of risk in production
- 100 fold reduction of risk by testing

- 56% (15 M litres) of the world supply of plasma (26.5 M litres) comes from North America (2008)
- Current pricing is ca. \$148/litre
- Range \$140 - \$160 (2008)
(MRB April 2009)
- Collection + testing >\$100/litre



Recalls, withdrawals, quarantines



- 1997/1998 vCJD effect
- 5-10% reduction in IVIG output from quarantine or destruction in 1997
- End product manufacturing limited by withdrawals and quarantines

- Qualified donors: 2-4% drop in collections
- 1.2% of collections destroyed
- Hold cost: + \$0.25/L
- NAT testing: +\$5-\$15/L
- Minipool testing
- Retesting of final products



Processing safety: safety adds cost

TSE clearance

Specific viral inactivation/removal steps add cost:

- Cost for the step
- Cost for the additional steps
- Cost for the work in progress

Table 1. Flebogamma® 5% DIF[™] Reduction Factors (RFs) and Overall Reduction Capacity (log₁₀/ml)

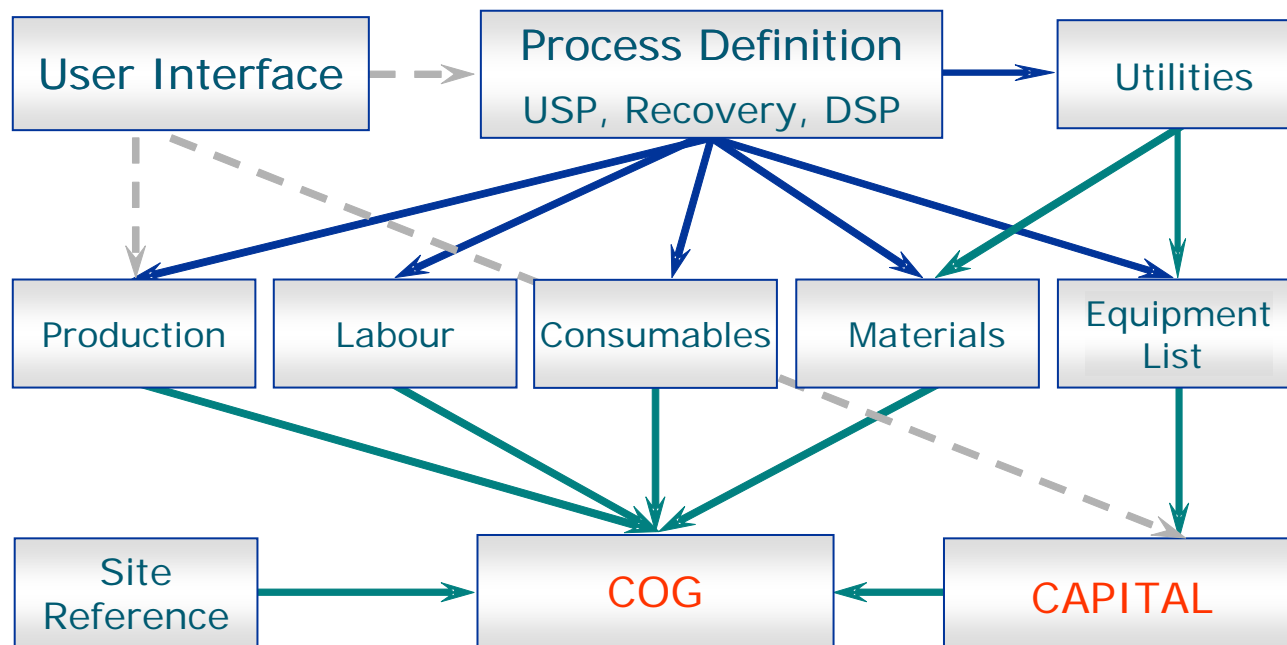
Target virus	HIV-1, HIV-2 (env. RNA)	HBV, Herpesvirus (env. DNA)		HCV (env. RNA)		WNV (env. RNA)	HAV (non-env. RNA)	B19 virus (non-env. DNA)
		PRV	IBR	BVDV	SINDBIS			
Model virus	HIV-1	PRV	IBR	BVDV	SINDBIS	WNV	EMC	PPV
Fraction I precipitation	<1.00*	nd	nd	nd	nd	2.78	nd	nd
Fraction II+III alcohol incubation	1.48	nd	nd	nd	nd	< 1.00*	nd	nd
4% PEG precipitation	≥ 6.10	≥ 5.92	nd	≥ 5.78	nd	nd	≥ 6.41	6.35
pH 4 treatment	2.47	≥ 5.32	nd	<1.00*	nd	nd	1.36	na
Pasteurization	≥ 5.64	nd	≥ 6.33	nd	≥ 6.49	≥ 5.42	≥ 5.56	4.08
Solvent Detergent	≥ 4.61	≥ 6.95	nd	≥ 6.14	nd	≥ 5.59	na	na
Double nanofiltration (35 nm + 20 nm)	a	a	a	a	a	a	a	4.61
Overall Reduction Capacity	≥ 20.30	≥ 18.19	≥ 6.33	≥ 11.92	≥ 6.49	≥ 13.79	≥ 13.33	15.04

a) During the nanofiltration validation, 9 different viruses (HIV, PRV, BVDV, WNV, EMC, SV40, BEV, Echo 11 and PPV) were evaluated. Eight of these viruses were inactivated by the process conditions and/or removed by prefiltration. Only PPV, the virus of smallest size, was affected neither by the filtration conditions nor by the prefiltration.

Instituto Grifols, S. A. Barcelona, November, 2006



Capex/Opex calculation model





Revenue calculation summary

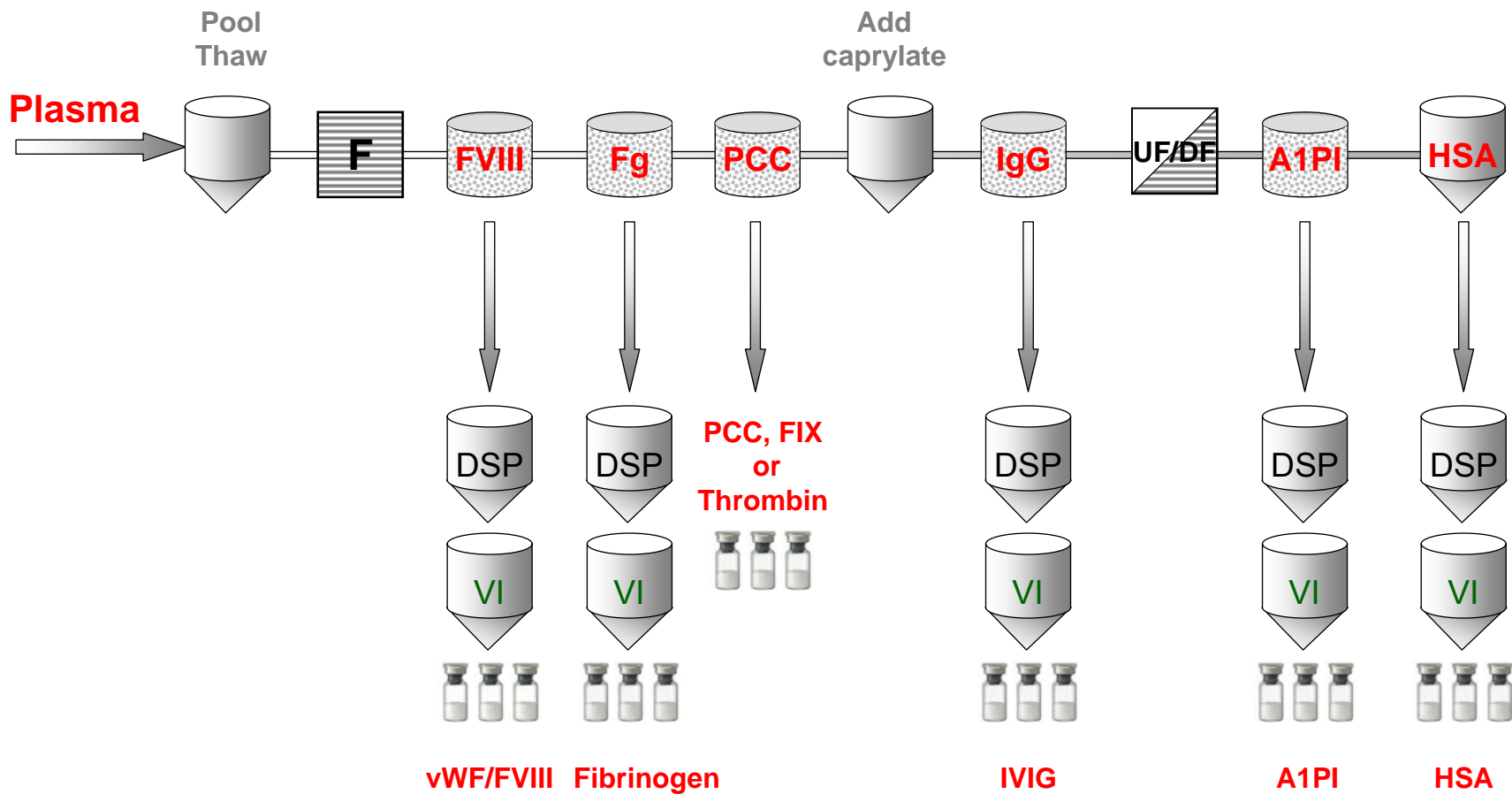
Product	Plasma conc./L	Yield, g or IU/L	Yield, %	US\$/g or IU	Revenue/L (Potential)	Revenue/L (Adjusted)
vWF/Factor VIII	1,000 IU	450 IU	45%	0.7	\$315	\$158 (50%)
IVIG	8 g/L	5.6	70%	70	\$392	\$392
A1PI	1.2 g/L	0.8	67%	400	\$320	\$64 (20%)
HSA	35 g/L	25	71%	4	\$100	\$100
Total potential revenue/litre plasma					\$1,127	
Total adjusted revenue/litre plasma						\$714

vWF/FVIII calculated as FVIII:C

- CSL: A\$ 900/litre plasma, currently US\$640
 - Talecris: A\$ 580/litre plasma, currently US\$413
- (Helen Cameron of Citigroup, quoted by Bloomberg, August 2008)*



PPPS: Process flow sheet





Basic unit operations

	Number	% of total
Bind-elute chromatography	5	14%
Flow-through chromatography	5	14%
Filtration (clarification)	4	11%
TFF (UF/DF)	9	26%
Nanofiltration	2	6%
Sterile filtration	4	11%
Others (incl. precipitation)	6	17%
Total	35	100%

- 2/3 of all operations are membrane based
- <1/3 are chromatographic



Input variables

- 100,000 litre or 500,000 L annual plasma throughput capacity
- Capacity utilization ca. 100%
- At 100,000 L: 450 litre lot size, started 5 times/week
- At 500,000 L: 2,200 litre lot size, started 5 times/week
- 45 weeks operation/year
- Operator hours/week = 40

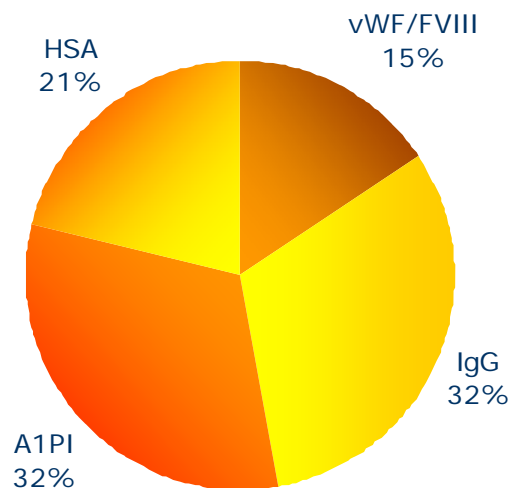
- Concentrated solutions prepared for 5 batches
- Disposable options for product and solution hold up to 3,000 L
- Liner disposable system



Capital cost summary

Description	Investment cost	
	100,000 litres	500,000 litres
Equipment	\$13.4 M	\$ 21.4 M
Sub-contractors	\$35.0 M	\$ 58.4 M
Total Cost of Works	\$48.4 M	\$ 79.8 M
Engineering fees + Validation	\$16.9 M	\$ 27.9 M
Total Project Cost	\$65.3 M	\$ 107.7 M

Investment by product





Engineering and validation fees: 100,000 L

Cost category	Engineering ratio*
Validation costs	15%
Engineering fees	20%
Total fees	\$28 M

*Experience based engineering ratios provided by BioPharm Services
As % of Cost of Works - \$79.8 M

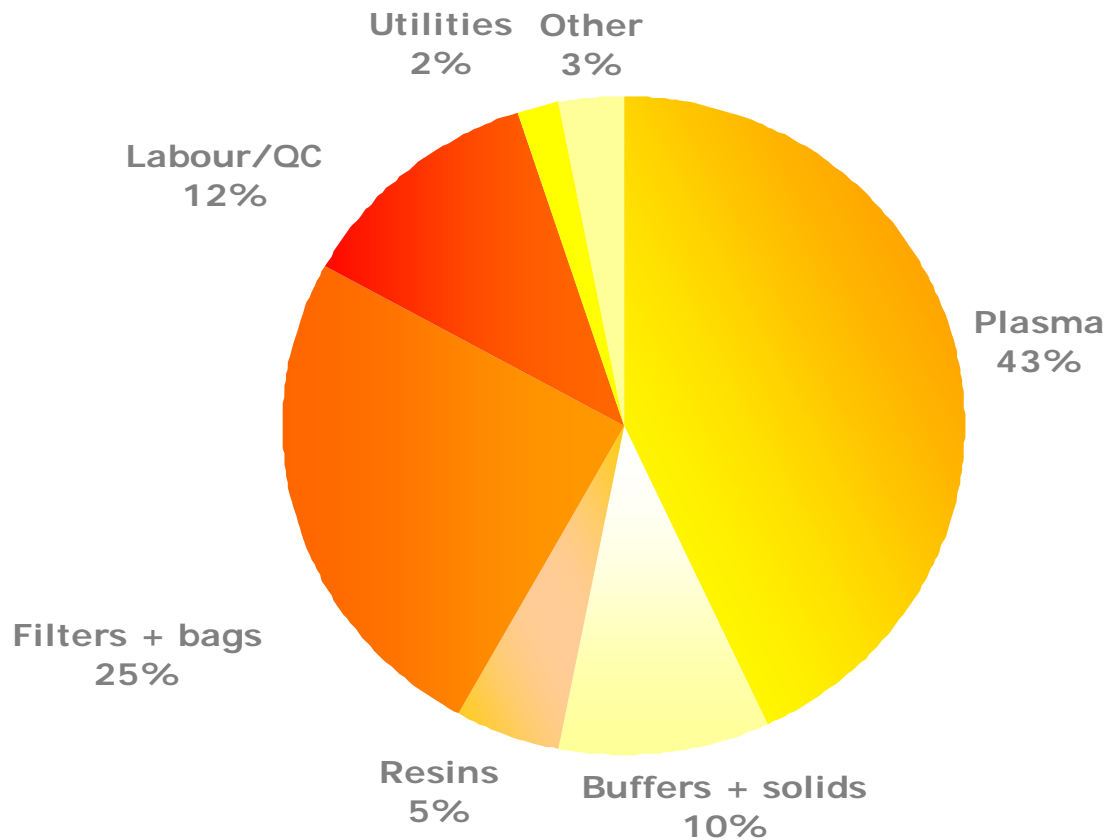


Capital cost references

Company	Capacity, Litres	CAPEX, US\$, M	Date
Alfa Laval Biokinetics/ProMetic	500,000	\$129	PPB 2005
BioPharm Services/ProMetic	500,000	\$107	PPB2009
Contractor	500,000	\$100 -125	2007
Kedrion/Glatt Engineering, Russia	300,000 up to 600,000	\$119	Feb. 2006
Jeddah Biotechnical Co., Saudi Arabia	500,000	\$200	March 2007
NACO/Govt. of India (Chennai?)	150,000	\$37 (Rs 185 crore)	Oct 2008
Intas (Celestial Biologics) (GE)	150,000 up to 300,000	\$20	Jan 2009



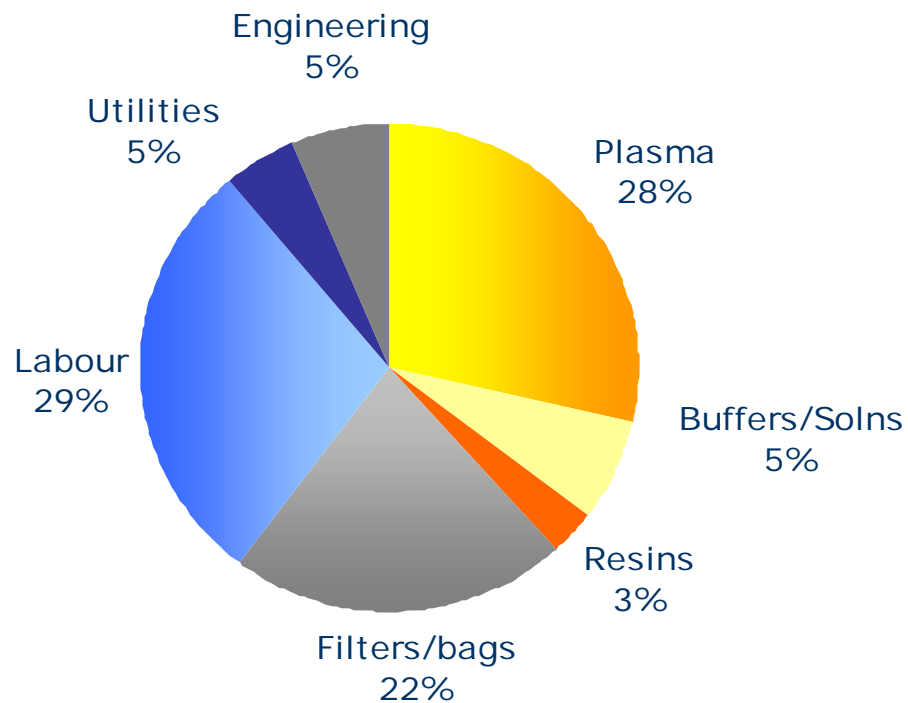
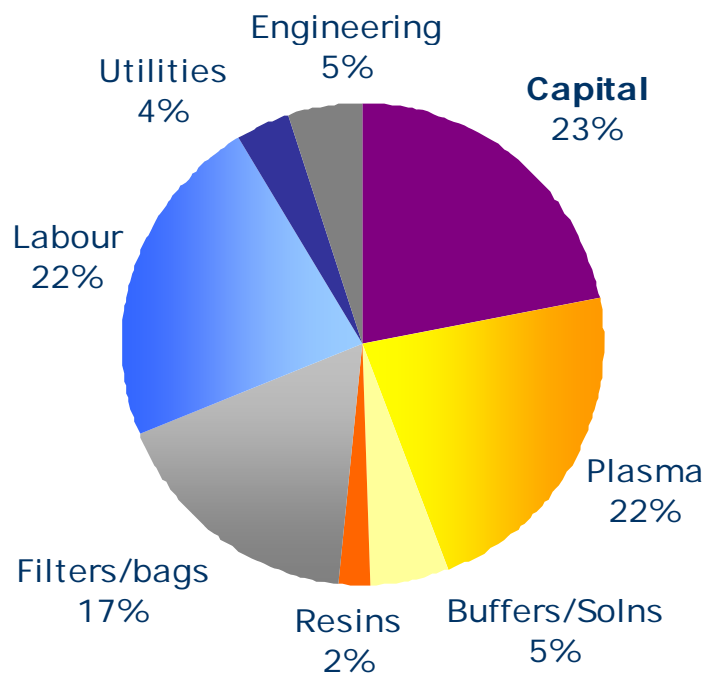
Cost distribution at 500,000 litre scale



Cost distribution per litre plasma fractionated at 500,000 litre plant capacity, excluding capital costs
Batch size: 2,200 litres. Plasma = \$120/litre. Fractionation cost = \$154. Σ = \$274



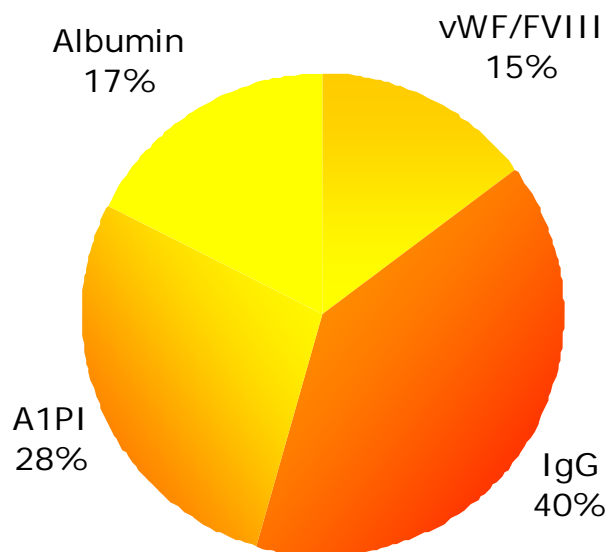
Distribution of costs at 100,000 L





Cost per gram of product at 100,000 L

- Excluding capital
- Plasma cost allocation: vWF/FVIII 20%, IgG 40%, A1PI 20%, Albumin 20%

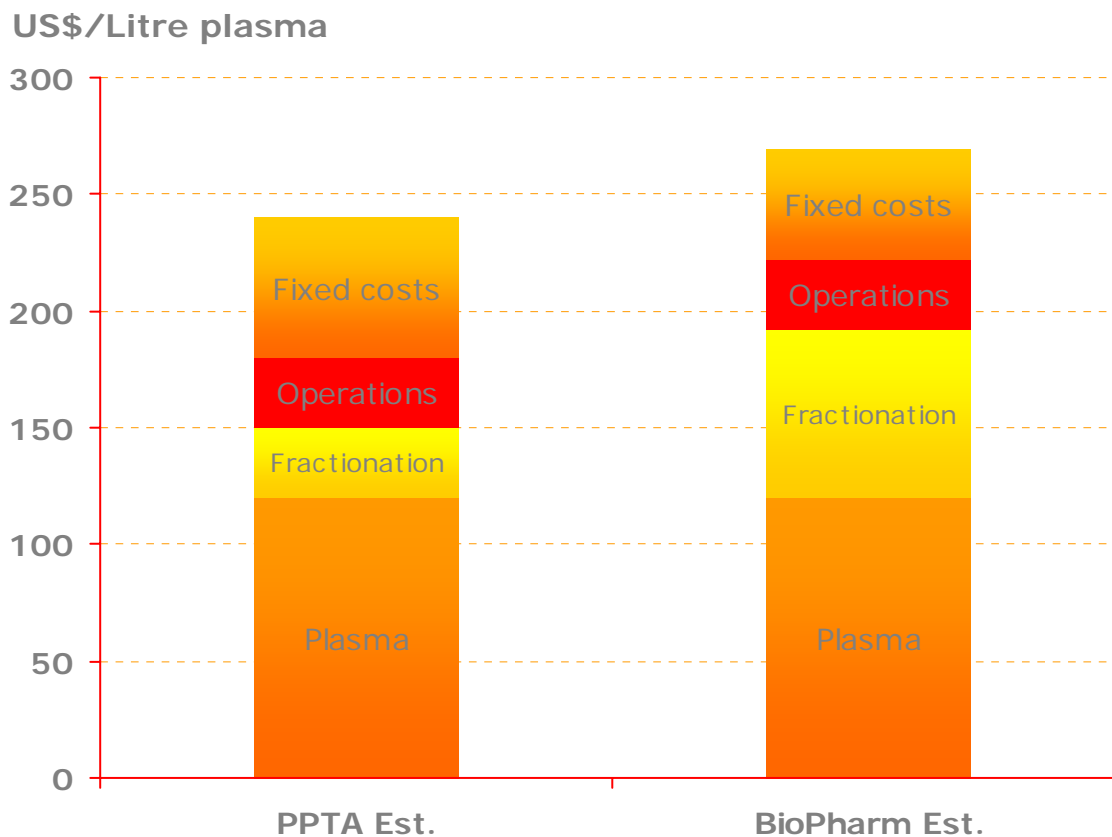


Product	Cost, \$/g	Revenue, \$/g
vWF/FVIII	23,741	3.5 M*
IgG	29	70
A1PI	147	400
HSA	3	4

* Equivalent to \$0.7/IU



Costs compared to PPTA model



Cost distribution per litre plasma including capital costs.
PPTA costs adapted from Bult, J. IPPC, Warszawa 2008.
PPPS costs from BioPharm Services model, January 2009



Costs at different scales

Values in US\$	Scale, L			
	10,000	100,000	500,000	Grifols*
Cost/g IgG	64	31	23	27.0
Cost/g HSA	9	4	2	1.46
Cost/g FVIII	60,000	27,000	17,000	0.16/IU

	Scale, L			
	10,000	100,000	500,000	Grifols*
Cost/L IgG	33%	37%	48%	51%
Cost/L HSA	19%	19%	16%	21%
Cost/L FVIII	14%	15%	15%	20%

* Financing plasma proteins: Unique challenges, Pharmaceuticals Policy and Law 2005/2006



CAPEX/OPEX cost summary

Values in US\$

	Scale, L		
	10,000	100,000	500,000
Total CAPEX	52.5 M	68.5 M	108 M
Total OPEX*	1,095/L	476/L	274/L

* Includes plasma @ \$120/L, excludes capital charge

Grifols reports fractionation cost range of €120 - €140/L

Financing plasma proteins: Unique challenges, Pharmaceuticals Policy and Law 2005/2006



The low CAPEX model – Myth or reality?

Cost category	BioPharm	CAPEX \$ M		
		Contractor	Low cost alt.*	% discount
Process equipment	15.5	14	7	50%
Process utilities	5.6	14 incl. HVAC	7	50%
Installation + Pipework	17.8	13	7	50%
HVAC	7.1			
Instrumentation + Control	12.1	13	7	50%
Electrical power	5.2			
Building + fit out	16.4	35	11	70%
Fees and validation	28.0	12	6	50%
Total	\$107.7 M	\$101 M	\$45 M	

* An Indian dream?



Capital costs - 500,000 litre plant

Type/Use of equipment	CAPEX \$ M
Backbone fractionation	4.8
Downstream processes	6.9
Process vessels	2.8
Bag/Mixer systems	0.3
Others	0.5
Process utilities	5.8
Cleaning	1.0
Total equipment cost	21.3

- Original manufacturers
- Buy, reverse engineer
- Own clones for multiple units

- Local design
- Local manufacturing

Data is summed from detailed equipment sizing lists and process operation details
Data collected from ProMetic, Sartorius, GE, Teknikrom etc. and BioPharm Services database



Sub-contractor capital costs: 100,000 L

Cost category	CAPEX \$ M
Installation + Pipework	17.6
HVAC	7.1
Instrumentation + Control	12.1
Electrical power	5.2
Building	13.4
Fit out	3.0
Total sub-contractors	\$58.4 M

- OEM
- Local design
- Local fabrication

Experience based engineering ratios provided by BioPharm Services
As % of Equipment Cost - \$21.3 M



Labour costs and opportunities

Personnel	Salary
Production supervisors	\$68,000
Production and Engineering	\$60,000
Administration etc.	\$40,000
Laboratory staff	\$48,000
QA/Regulatory affairs	\$61,500
Validation	\$64,000
<i>Overhead calculated at</i>	<i>55%</i>

Personnel	Number
Production supervisors	153
All others	53
Total	206

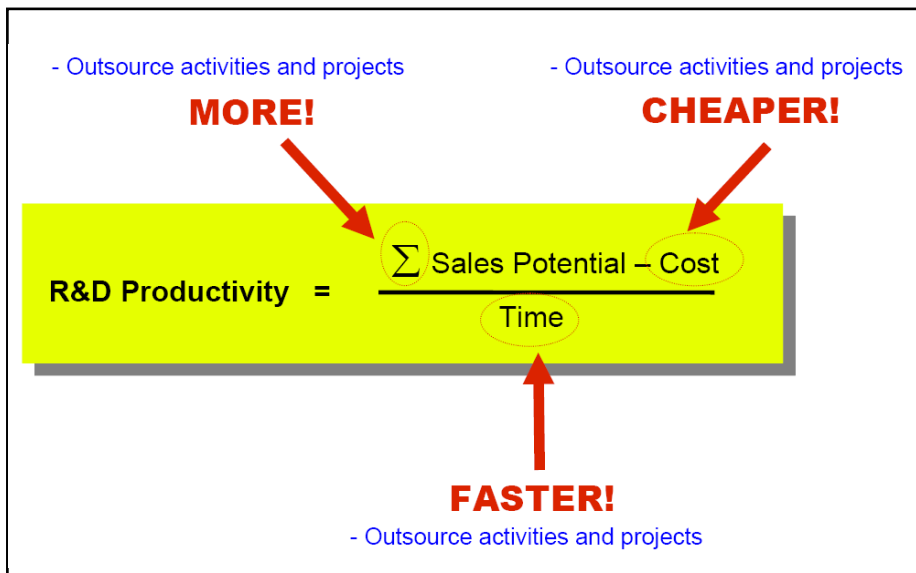
500,000 Litre Plant





Design opportunities and fear of the new

- Made in India
- Designed in India?
- Made in China
- Designed in China?



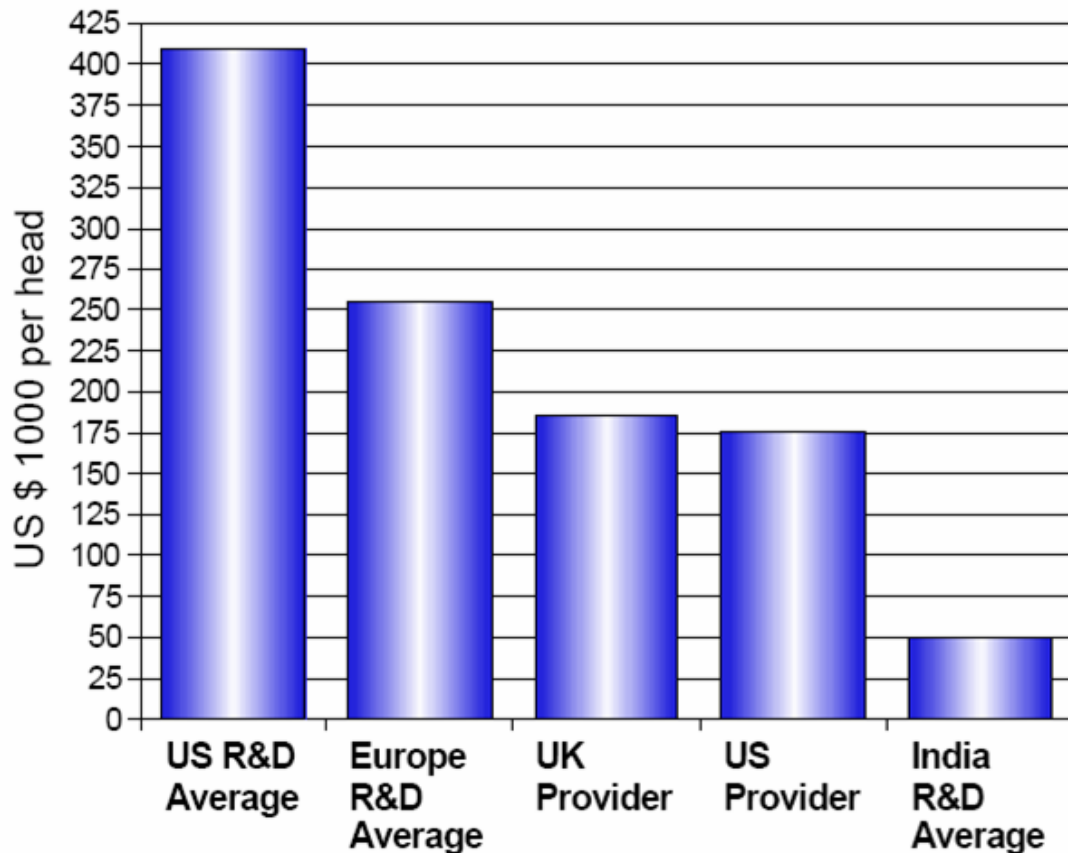
Antonio Gaudi, Casa Batlló, Barcelona (1905-1907)

Diagram from: Mottl, H. 3A Global Markets. Opportunities for outsourcing, Cambridge, 2005.



Comparative R & D cost opportunities

- Discovered, researched, developed, manufactured and marketed?



Mottl, H. 3A Global Markets. Opportunities for outsourcing, Cambridge, 2005.



Comparison with outsourcing, risks

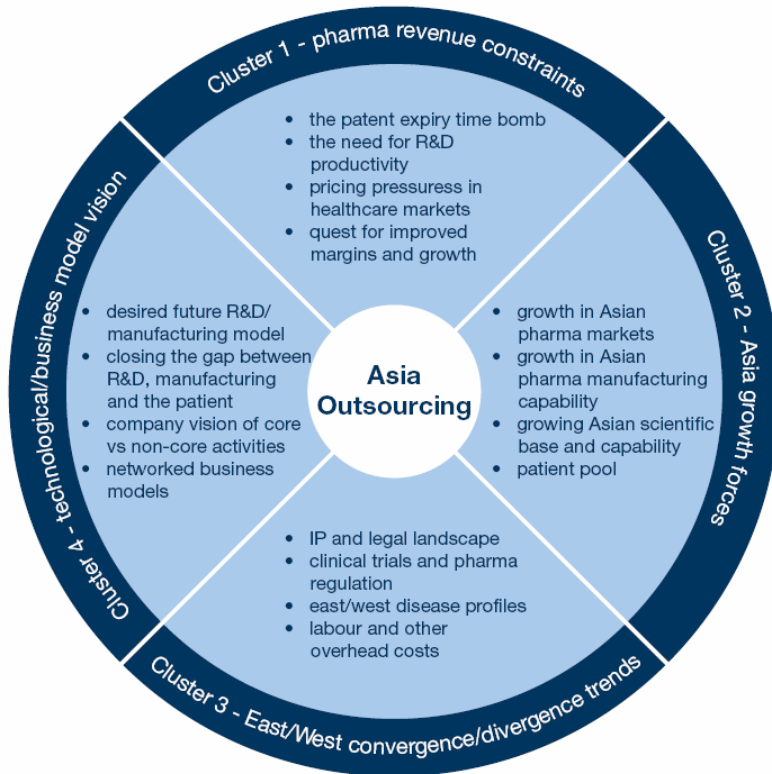
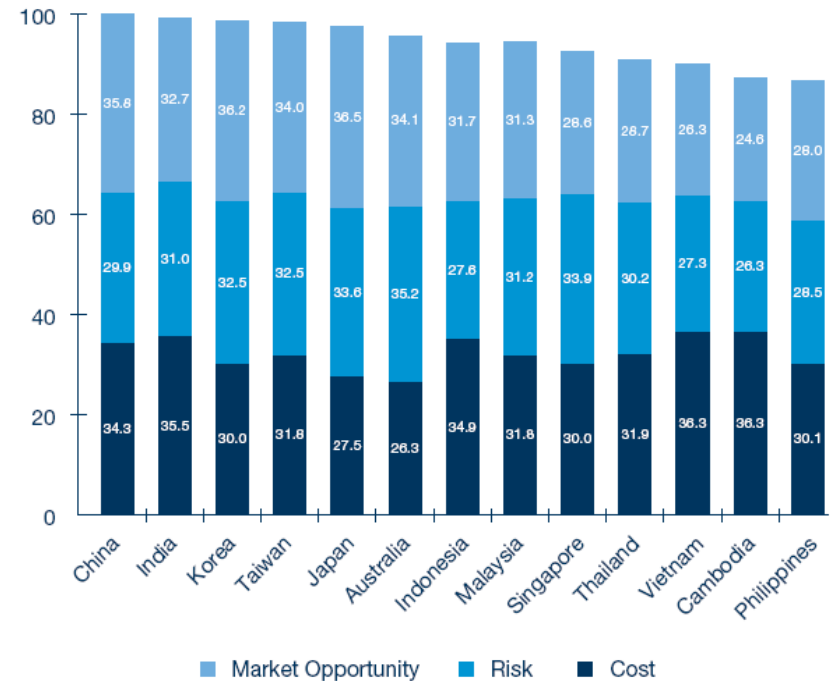


Figure 3: Outsourcing index - ranking of Asian territories across all factors



(Scores are 'normalised' with the best ranking territory = 100. Thus, higher scores indicate lower costs, lower risks and greater market opportunity.)

PricewaterhouseCoopers: The changing dynamics of outsourcing in Asia, 2008



Engineering risks are everywhere



Baxter Bioscience, Desmet, B, PPB 09, Elba 2007

"Microstructure quality is a major issue with 316L stainless steel. The metallurgical quality of alloys is an important issue since it has a direct impact on the corrosion resistance and therefore on product contamination. The presence of discontinuities on surfaces resulting from removal of inclusions that intersect the surface can release contaminants that in turn affect product quality and yields."

Ahluwalia, H., Uhlenkamp, BJ., Pharmaceutical Technology, March 2, 2008



Figure 3: Typical microstructure of a 316L plate that is common in the market. The microstructure has stringers of delta ferrite in the microstructure. The sample is etched in sodium hydroxide.

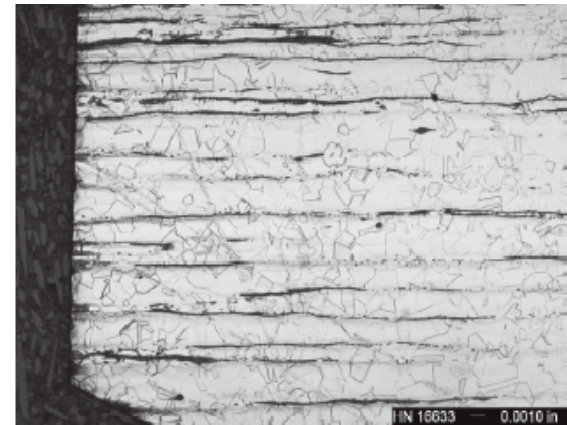
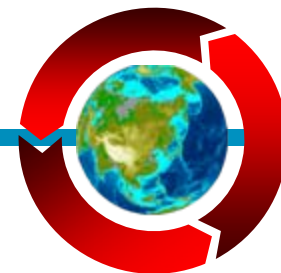


Figure 4: Microstructure of 316L bar product showing stringers of manganese sulfide inclusions that are not desirable for biopharmaceutical equipment.



Quality risks – still learning



" I don't understand what's wrong with yesterday's quality"
(R & D Director, Biopharmaceuticals)

- 1820 US Pharmacopoeia established
- 1902 The Biologics Control Act – purity and safety of sera and vaccines
- 1906 Food and Drugs Act
- 1933 – 1938. Revision of 1906 Act, "Elixir of sulfanilamide" incident (1937), The Federal Food, Drug, and Cosmetics Act (1938)
- 1941 "Sulfathiazole" incident leads to establishing GMP
- 1941 Insulin amendment – FDA must test and certify **purity and potency**
- 1945 Penicillin amendment – FDA must test **safety and efficacy**
- 1952 "Chloramphenicol" incident leads to **adverse event reporting**
- 1953 Factory **Inspection** Amendment
- 1962 "Thalidomide". Introduction of **approval for sale**
- 1972 Regulation of biologics – sera, vaccines, blood products transferred from NIH to FDA
- 1983 Orphan Drug Act
- 1997 FDA Modernization Act
- 2005 Drug Safety Board

- 21stC: New FDA paradigms: Critical path, evidence-based, PAT, QbD
- Don't forget ICH!



Regulatory challenges



In the last analysis, it is our conception of death which decides our answers to all the questions that life puts to us.

Dag Hammarskjöld, UN Secretary-General, 1953-1961

	Population Millions	Under \$1/day	Per capita expense	Life expectancy	Infant mortality
USA	302.8	-	\$3,074	69	7
Spain	44	-	\$1,641	73	4
India	1,151	34.3%	\$8	53	57
China	1,328	9.9%	\$38	64	20

Health indicators
WHOSIS

	USA	Spain	India	China
Communicable	52.6	41.3	366.2	73.6
Non-communicable	722.4	773.1	462.6	562
Injuries	56.8	33.6	106.1	72

Deaths/100,000 (2004)
WHOSIS

Acknowledgement

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