4th Plasma Product Biotechnology Meeting
Porto Elounda, Crete, Greece, 9-12 May 2005

A New, High Yielding, Affinity Cascade for Sequential Isolation of Plasma Proteins of Therapeutic Value

Christopher Bryant, Dev Baines, Ruben Carbonell, Tom Chen
John Curling, Timothy Hayes, Steve Burton, David Hammond

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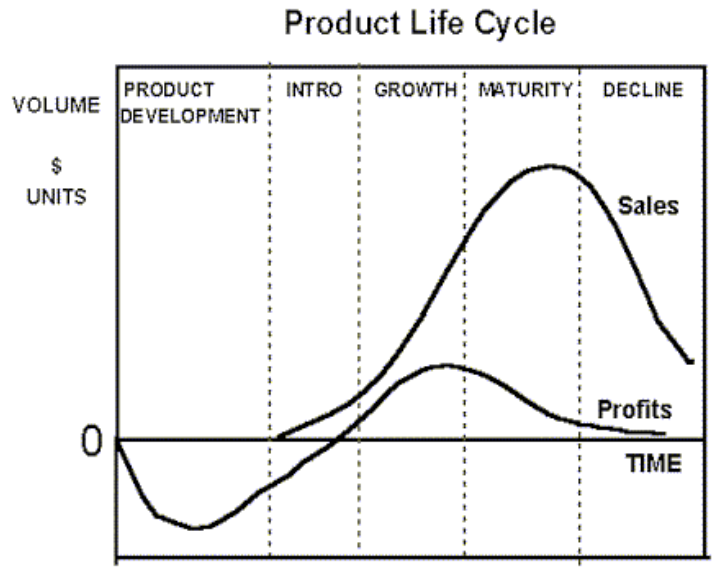
OPTIMISING PLASMA FRACTIONATION

Plasma Protein Industry - A Truly Ambiguous Future ?

(C. Bryant - PPB2003, Curacao)

- Perception that This is a “Mature” Industry
- Conventional Business Wisdom Dictates:
  - Rationalize R&D Investment
  - Implement “Life Cycle Management” Programs
  - Decrease Investment in Innovation
- Milk the “Old Cow” Until it Dies!
- A True “Innovators Dilemma”
  - **Now** is the Time to Abandon Conventional Business Wisdom and Begin Adopting “Disruptive Technologies” versus “Rational Investments”



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Innovators Dilemma Principle#1
Companies Depend on Customers and Investors for Resources

- While Managers May Think They Control the Flow of Resources, in the End it is Really Current Customers and Investors Who Dictate How Money is Spent
- The Highest-Performing Companies Are Those that Are Best at Killing Ideas That Their Current Customers Don't Want
- As a Result , These Companies Find it Difficult to Invest Adequate Resources in Disruptive Technologies i.e. Lower Margin Opportunities That Their Current Customers Don't Want (e.g. Emerging Markets) – Until They Want Them…And by then It's Too Late!
- The Only Instances In Which Mainstream Firms Have Successfully Overcome This Paradox, Is Where Autonomous Organizations—Free of Current Customers Needs– Are Established In Pursuit of Disruptive Technologies
- If It Can't Be Created Within…It's Time To Move "Outside the Box"!

PPPS – Plasma Protein Purification System
Collaborative Effort Between ProMetic and American Red Cross

- A sequence of unit operations based on differential surface interaction of protein solutes with a solid phase
- A sequence of affinity chromatographic adsorption steps
- Uses specifically designed synthetic ligand adsorbents
- Seven plasma proteins initially targeted
- Adsorbents designed for maximum binding of target protein
- Each adsorbent optimized for maximum recovery of non-bound proteins
- Column eluents can be compared to Cohn precipitates
- Sequences can be adapted to specific needs
- Sequence steps can be omitted if protein not required
- Downstream processes integrate viral reduction technology

ProMetic Life Sciences (PLI)

- ProMetic Life Sciences – parent company
- Corporate Headquarters in Montreal, Canada
- Listed on Toronto Stock Exchange (TSE)

- R&D spending CA$ 13.5 Million
- Business Units:
  - Enabling Technologies
  - Therapeutics
- Revenues Derived from Bioseparations Products and R&D Collaborations
- Bioseparations R&D - Cambridge, UK

Focus on Blood and Plasma Products with ARC

- Plasma Fractionation – ”Cascade process”
- Pathogen Removal and Detection Technologies

(www.prometic.com)

American Red Cross

The American Red Cross, a humanitarian organization led by volunteers, guided by its Congressional Charter and the Fundamental Principles of the International Red Cross Movement, will provide relief to victims of disasters and help people prevent, prepare for, and respond to emergencies.

- American Red Cross – non-profit organization
- Based in Washington DC, USA
- Disaster, Health and Safety, Biomedical, International, Services to military families and the community
- Operating expenses US$ 3.37 Billion, 2003
- Works with 3,850,000 volunteer donors in the USA
- Works with > 3,000 hospitals

Blood and Plasma Products

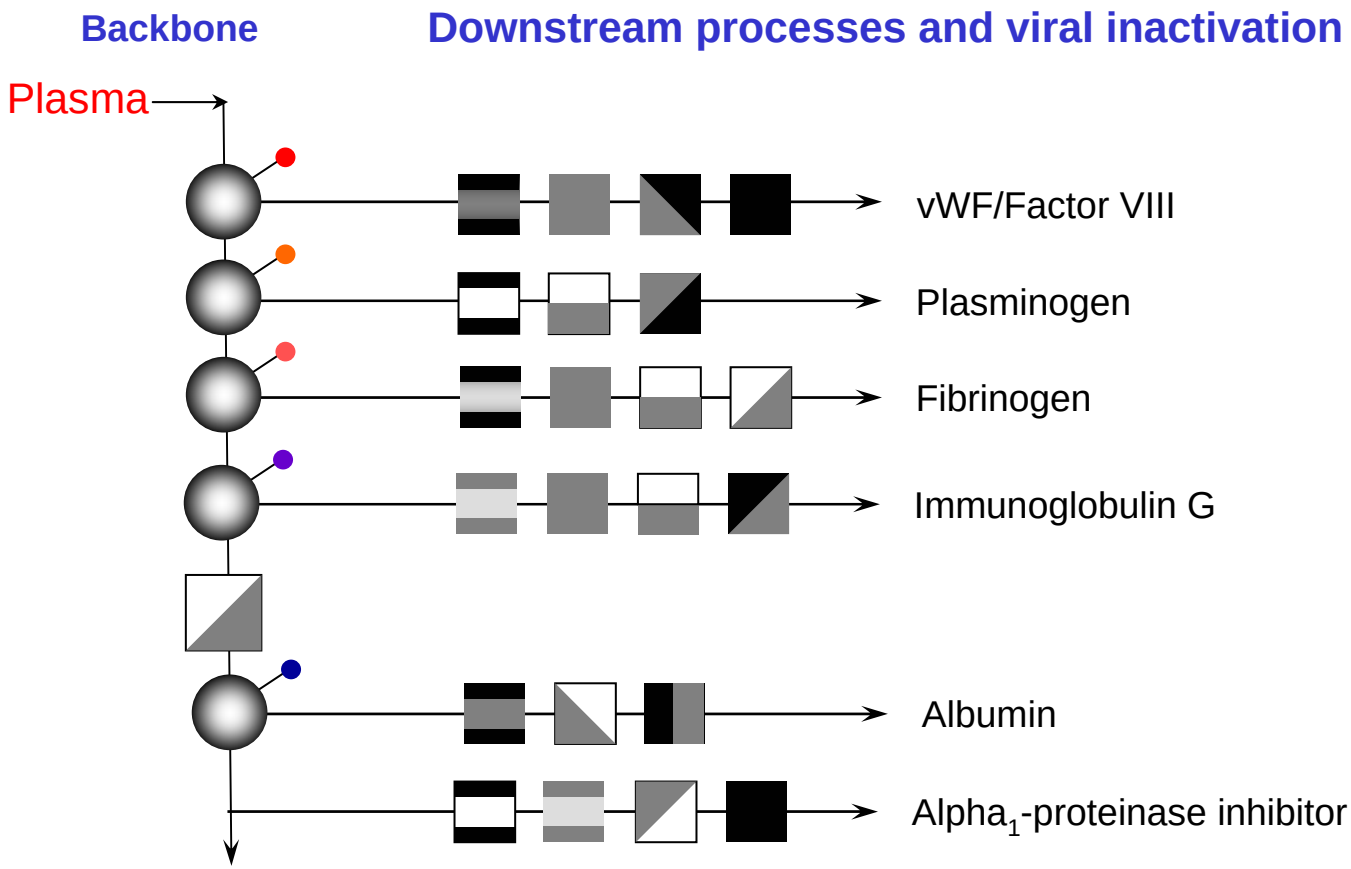
- Collected 6.42 million units in 2003
- Supplies almost 50% of the US need for blood – 38,000 units per day
- Conversion of Recovered Plasma in to Life Saving Protein Therapeutics
- Biomedical services account for ca. 60%, US$ 2 Billion Revenues

(www.redcross.org)

PPPS Keys To Success

- Ligand and Resin Development
  - ProMetic Core Competency
- Process Development
  - ARC / ProMetic Expertise
- Process Engineering
  - NC State / ProMetic / ARC / Hemosol
- BioAnalytical
  - ARC
- Market Development
  - North America -- Hemosol
  - Other Developed Market Opportunities -- EU
  - BRIC / ROW FOCUS

Cascade Process



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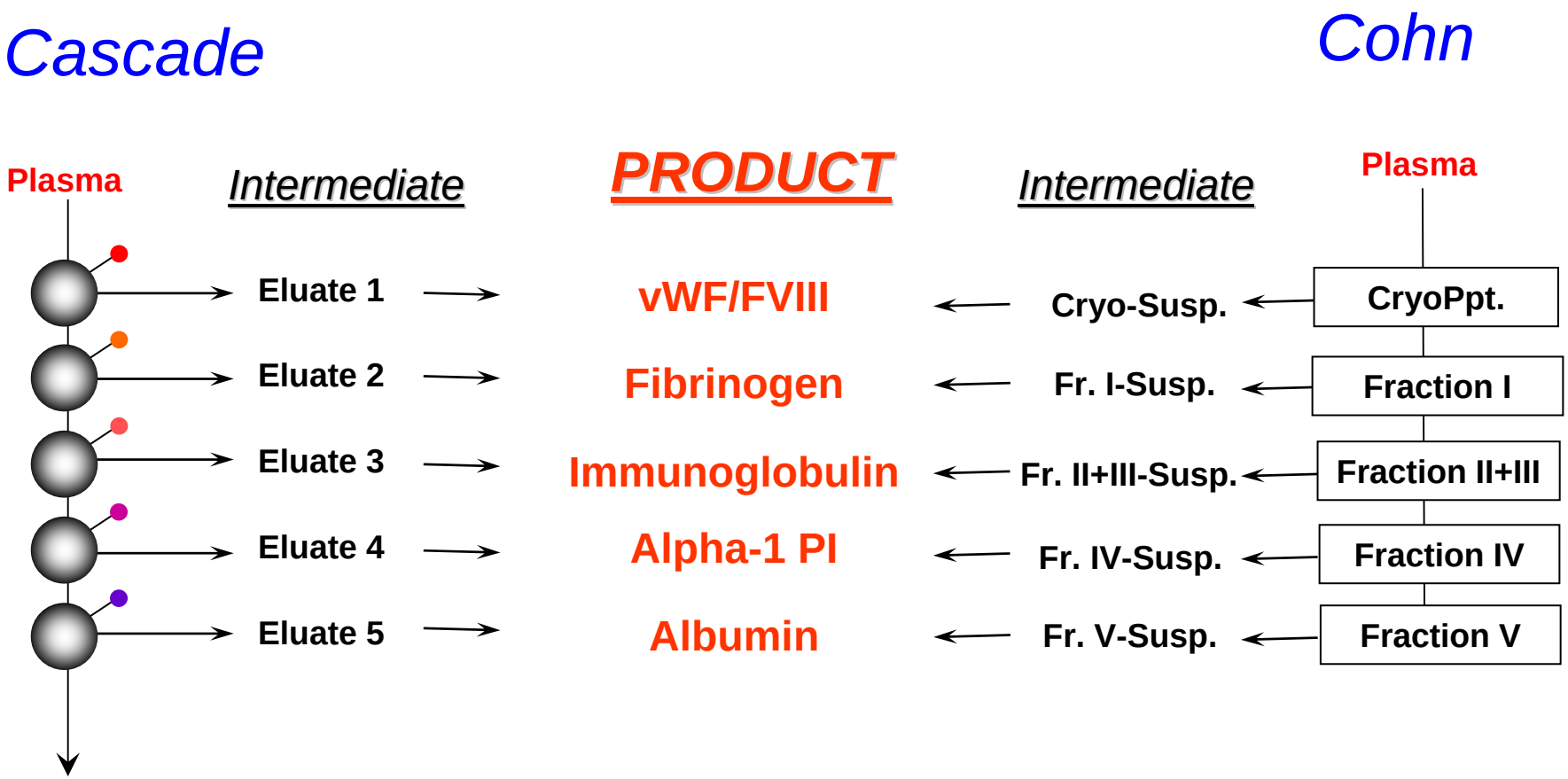
Cascade Technology Comparison to Cohn Process (I)

ProMetic-ARC Cascade Technology	Cohn (Oncley, Kistler-Nitschmann) Process
Designed for most needed proteins	Designed for albumin
Principle: Differential adsorption	Principle: Differential precipitation
Synthetic ligand affinity chromatography	Ethanol precipitation
Variables: pH, mS, buffer composition	Variables: pH, mS, ˚C, [Protein], [EtOH]
All protein targets kept in aqueous solution	Liquid-solid separation
No non-specific adsorbents	Precipitation aids necessary
Closed, highly automated system	Manual precipitate handling
Ambient temperature (controlled)	Zero and sub-zero temperatures, coolants
Direct capture of FVIII from plasma	FVIII by cryoprecipitation

Cascade Technology Comparison to Cohn Process (II)



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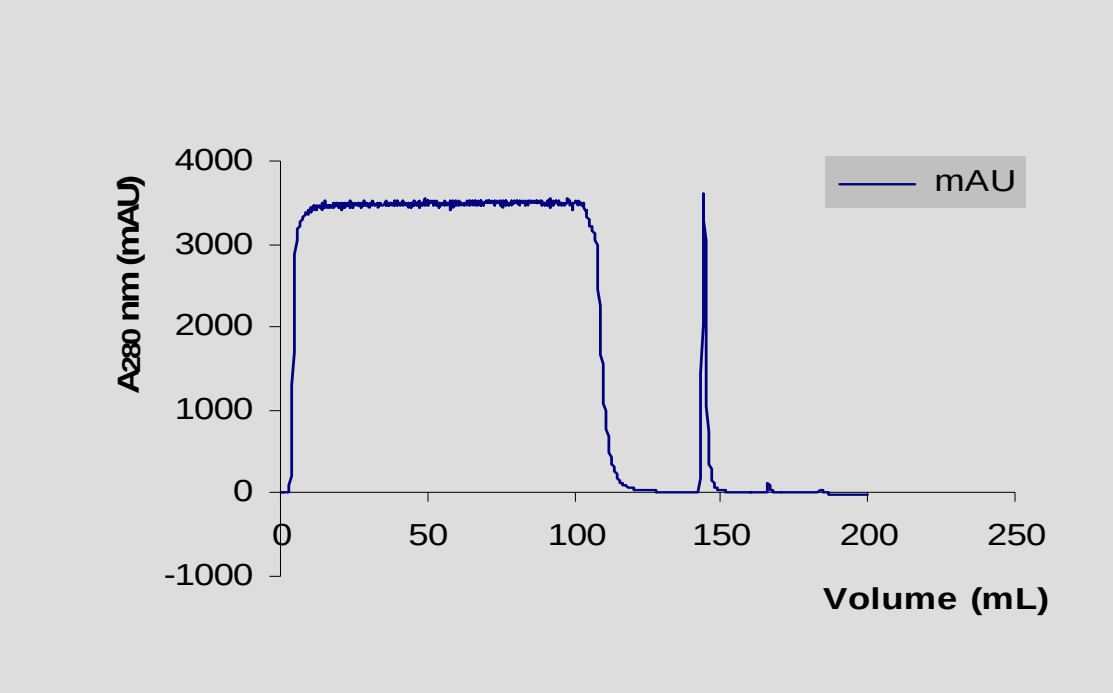
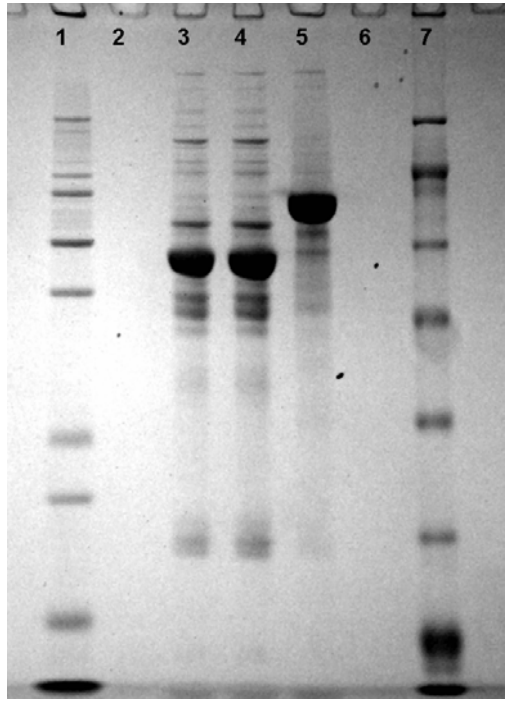
Cascade Technology Comparison to Cohn Process (III)

	Purity Specific activity/SDS-PAGE		Yield % Plasma input	
Target protein	Cohn Intermediate	PPPS Capture Eluate	Cohn Intermediate	PPPS Capture Eluate
vWF/FVIII	2 x 10^{-5} (cryo ppt.)	0.25	45	60
Protein "X" (confidential)	0 (Fr. IV ppt.)	0.45	0	50
Fibrinogen	0.65 (cryo ppt.)	0.74	40	80
Plasminogen	- (Fr. III ppt.)	0.79	35	77
IgG	0.53 (Fr. II + III ppt.)	0.50	70	87
Albumin	0.95 (Fr V ppt.)	0.94	85	85
A1PI	0.04 (Fr. IV ppt.)	0.25	23	90

Capture Purification – Plasminogen





4 mL column
Linear flow rate: 50cm/hour
Equilibration buffer: 50mM Sodium Phosphate pH 7.5 (5CV)
Load: 100 mL filtered human plasma
Post load wash buffer: 50mM Sodium Phosphate pH 7.5 (10CV)
Elution buffer: pH 7.5 (5CV)

Lane 1: MW Marker
Lane 2
Lane 3: Human plasma load
Lane 4: Flow through fraction
Lane 5: Elution fraction.
Lane 6:
Lane 7: MW Marker

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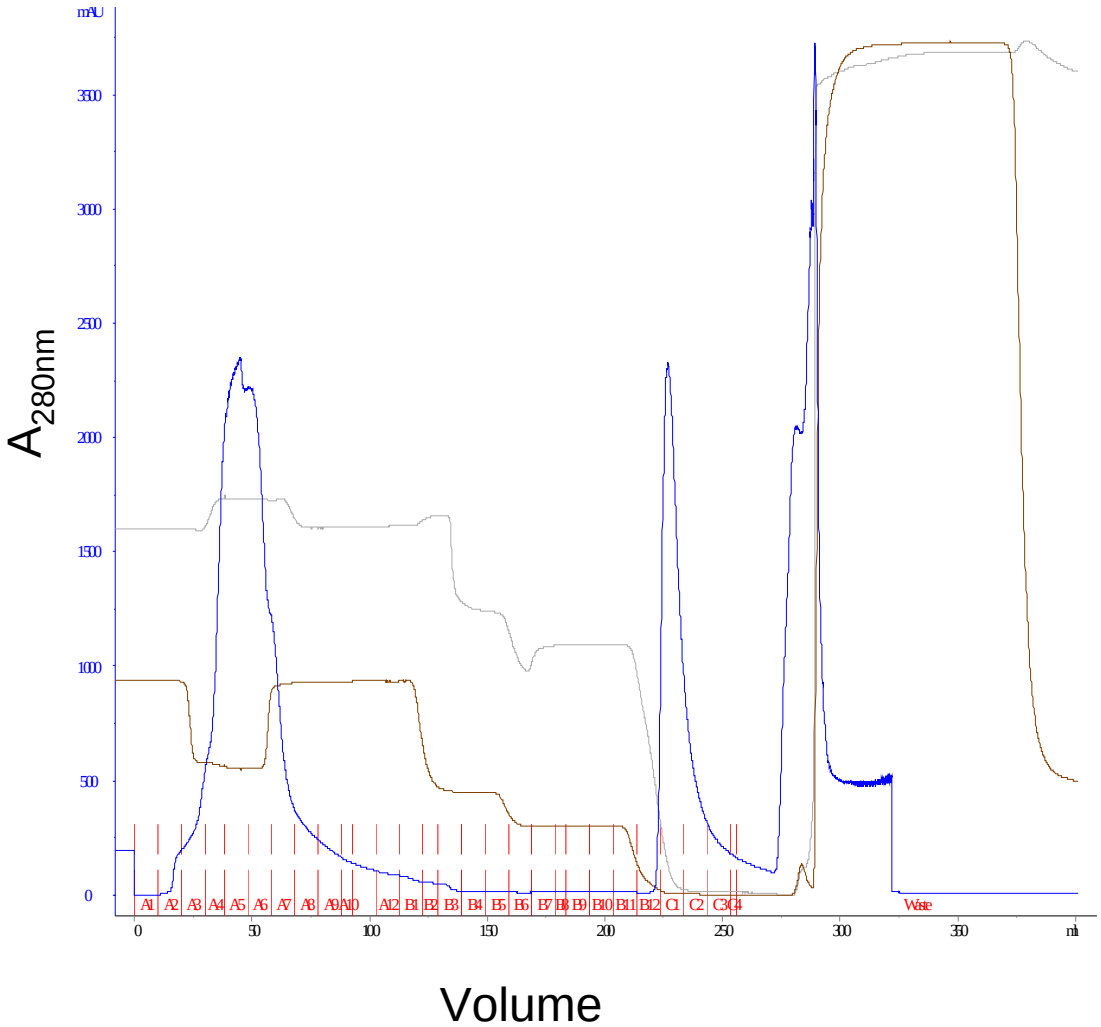
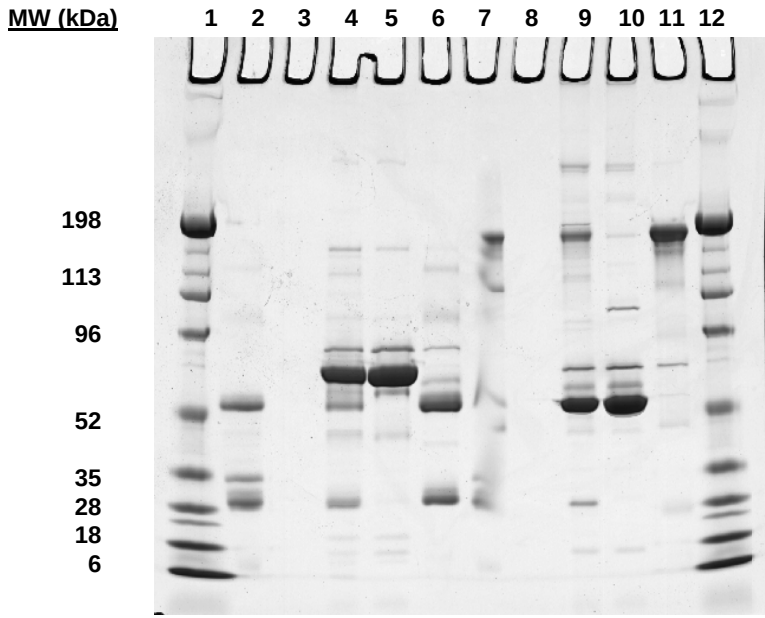
Cascade Purification - Immunoglobulin





Reduced -

- Lane 1: MW Broad Range Standard
- Lane 2: IgG Control
- Lane 3: Laemmli Buffer
- Lane 4: IgG load
- Lane 5: IgG Flow Thru
- Lane 6: IgG Elution

Non-Reduced -

- Lane 7: IgG Control
- Lane 8: Laemmli Buffer
- Lane 9: IgG load
- Lane 10: IgG Flow Thru
- Lane 11: IgG Elution
- Lane 12: MW Broad Range

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Anticipated Advantages - Process Economics

- Higher in-process yield presumably equates to higher final product yields
- Increased intermediate purity may reduce number of downstream purification steps required to achieve desired final product purity and thus a potential for increased final product yield
- Potential decreased operating costs:
  - Less plasma required for equivalent product volume
  - Processing temperature (25°C vs. -5°C)
  - Automated, closed systems requires less human intervention
  - No need for ethanol-solvent recovery infrastructure
- Enhanced cGMP environment = Less reject and re-work
- Opportunity to introduce innovations in pathogen reduction technologies may reduce necessity for costly plasma testing

Process Engineering Study Objectives

- Evaluate 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

Innovators Dilemma Principle#2
Small Markets Don't Solve the Growth Needs of Large Companies

Global GAP Between Supply and Demand

(R. Waeger-2003)

- **Approximately one million people rely on plasma protein therapies to live each year**
- **Many more have not been diagnosed or do not have access to therapies**

Consumer Community	Percent Treated	Percent Untreated
Hemophilia	20	80
Immunodeficiency	6	94
Alpha-1 deficiency	3	97

How to Fix the Global GAP

(R. Waeger-2003)

- Increased Manufacturing Capacity Through Investments in (new) Plants
- Increased Yields from New or Improved Processes
- New Products and New Applications

ProMetic and Hemosol Finalize their Strategic Alliance & Definitive License Agreement

HEMOSOL

- MONTREAL, June 2 /CNW Telbec/ - ProMetic Life Sciences Inc. (TSX: PLI) announces the closing of a definitive license agreement and strategic alliance……..
- Capitalize on Hemosol's GMP manufacturing expertise and ProMetic-ARC Cascade Process Technology
- Hemosol is the first of several of ProMetic's forthcoming licensees, and targets the North American demand".
- The alliance agreement aims at generating revenues for both companies on a short-term basis through technology transfer support and the supply of clinical trial material to other future licensees of ProMetic outside North America.

Journal of Thrombosis and Haemostasis, **1**: 1349–1355

REVIEW ARTICLE

Hemophilia: treatment options in the twenty-first century

P. M. MANNUCCI

Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Internal Medicine, IRCCS Maggiore Hospital and University of Milan, Italy

To cite this article: Mannucci PM. Hemophilia: treatment options in the twenty-first century. *J Thromb Haemost* 2003; **1**: 1349–55.

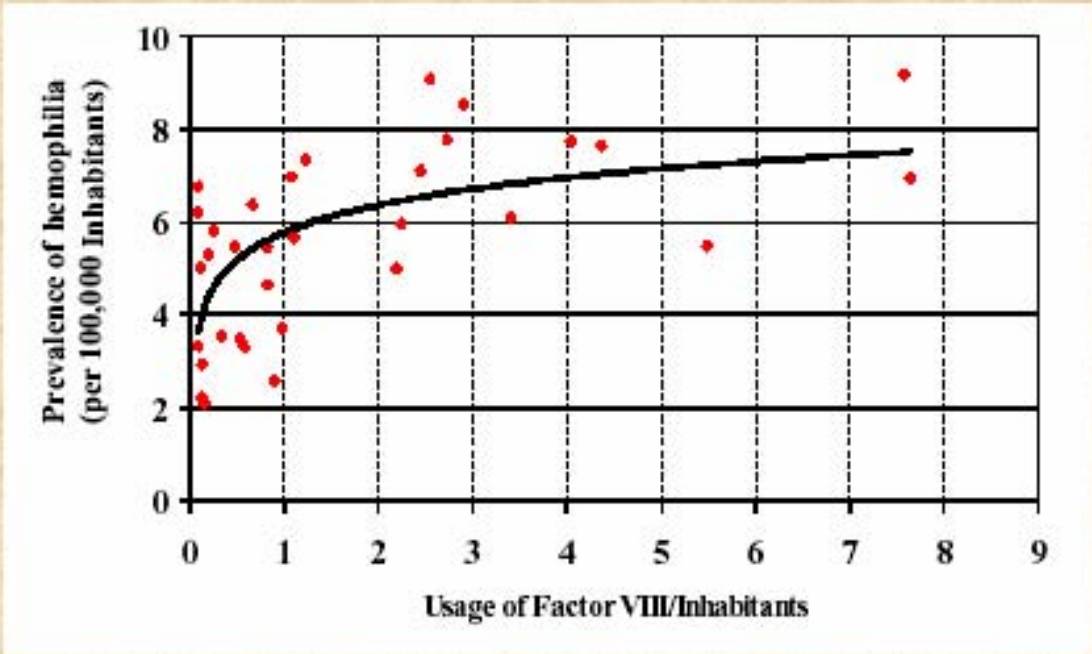
[20]. We recommended choosing recombinant factors first for newly diagnosed, previously untreated hemophiliacs and then for those who have been spared from blood-borne infections despite previous exposure to plasma-derived factors [21]. These restrictions and selection policies may change soon, as factor production is increasing and cost should decrease. It can be predicted that in the first decade of the twenty-first century replacement therapy will continue to evolve towards using more and more recombinant factors, at least in the richest countries.

On the other hand, one should make a point of reassuring the large number of persons with hemophilia that are using and will continue to use plasma-derived factors, the only foreseeable option for 80% of the persons with hemophilia worldwide who have at the moment no or limited access to any replacement material. The risks of blood-borne infections transmitted by plasma factors are more theoretical than real, and patients and policymakers should be educated to distinguish real from perceived risks. One would expect increased availability and

Progress is warranted in the quality of plasma fractionation technologies. The yield of FVIII from source plasma is still only 5–10%, a loss that is difficult to accept in an era of high technology!

Innovators Dilemma Principle#3
Markets That Don't Exist Can't Be Analyzed

OBSERVED PATIENT PREVALENCE AND AMOUNT OF FVIII USED IN 34 REPORTING COUNTRIES



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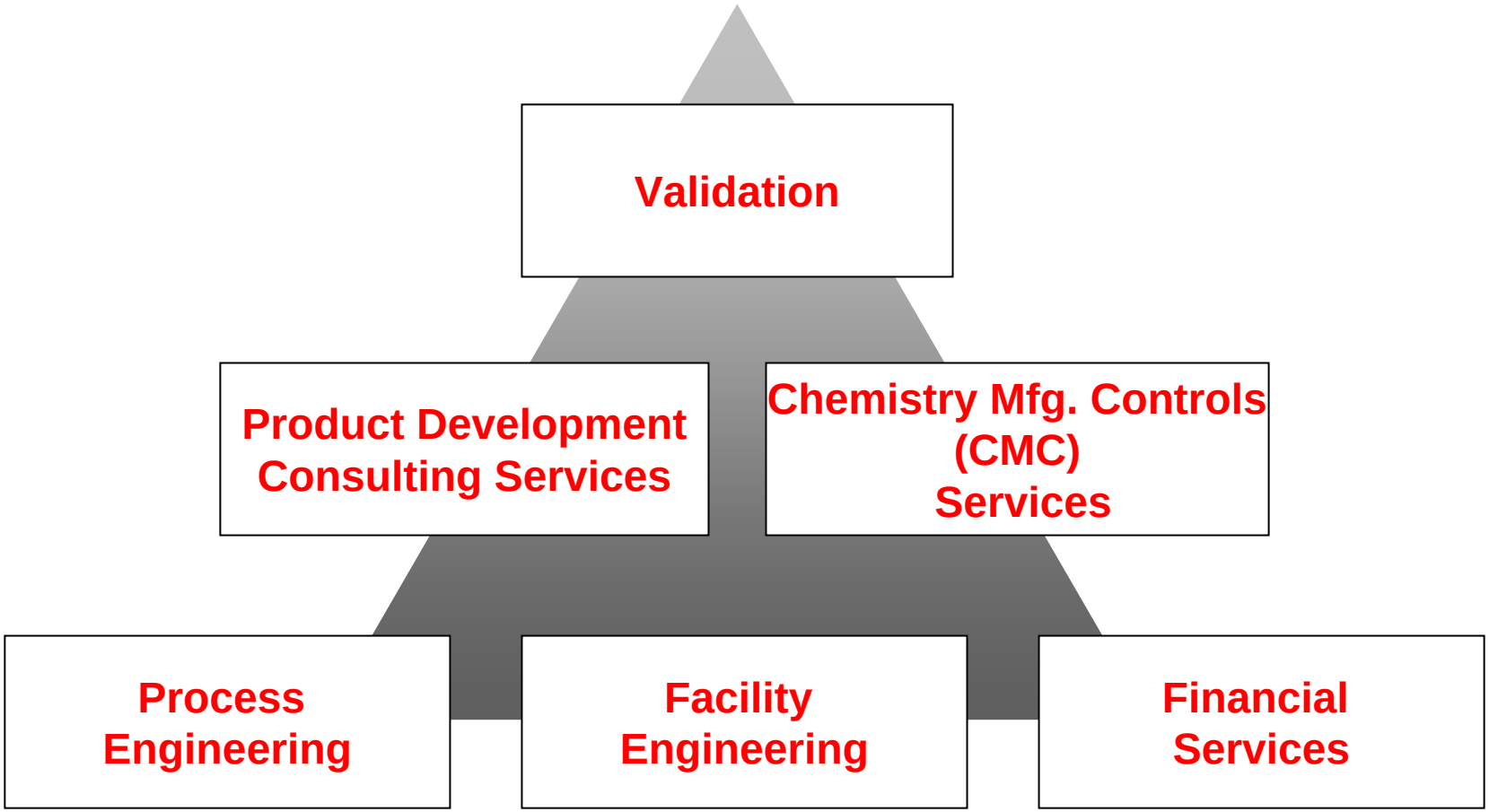
’’Turn-Key’’ Solution as a Technology Partner



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Innovators Dilemma Principle#5
Technology Supply May Not Equal Market Demand

Disruptive Technologies, Though they Initially can Only be Used in Small Markets Remote From Mainstream, Are Disruptive Because They Subsequently Can Become Fully Performance-Competitive Within the Mainstream Market Against Established Products

Plasma Protein Therapeutic Innovation

We're Ready…

ARE YOU?

OPTIMISING
PLASMA FRACTIONATION

Acknowledgements

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