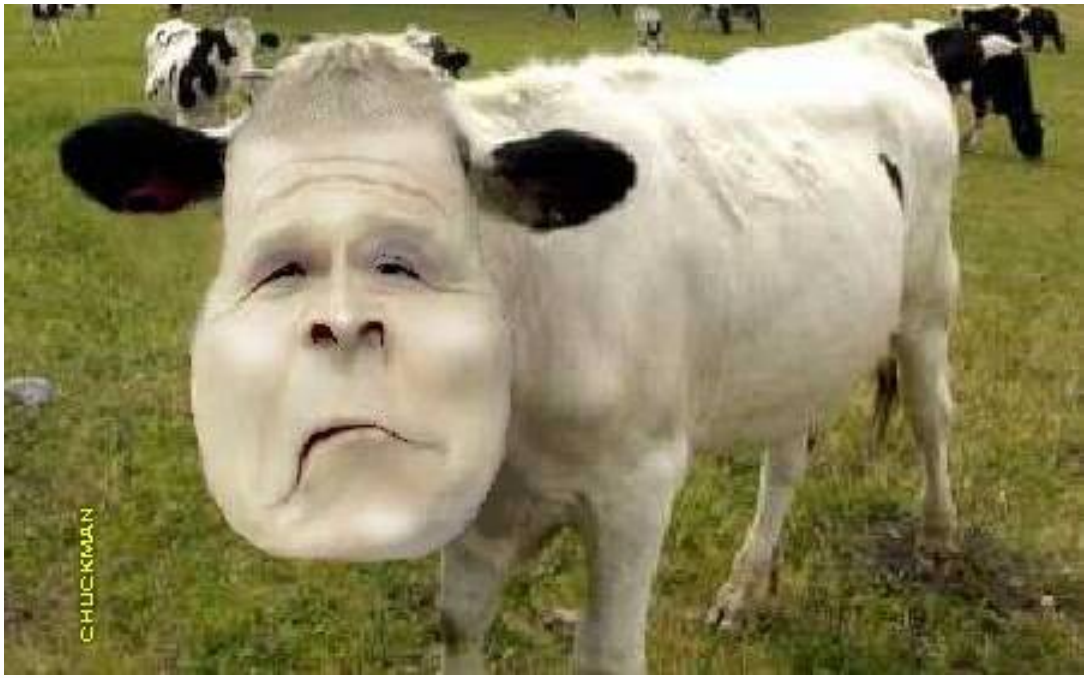


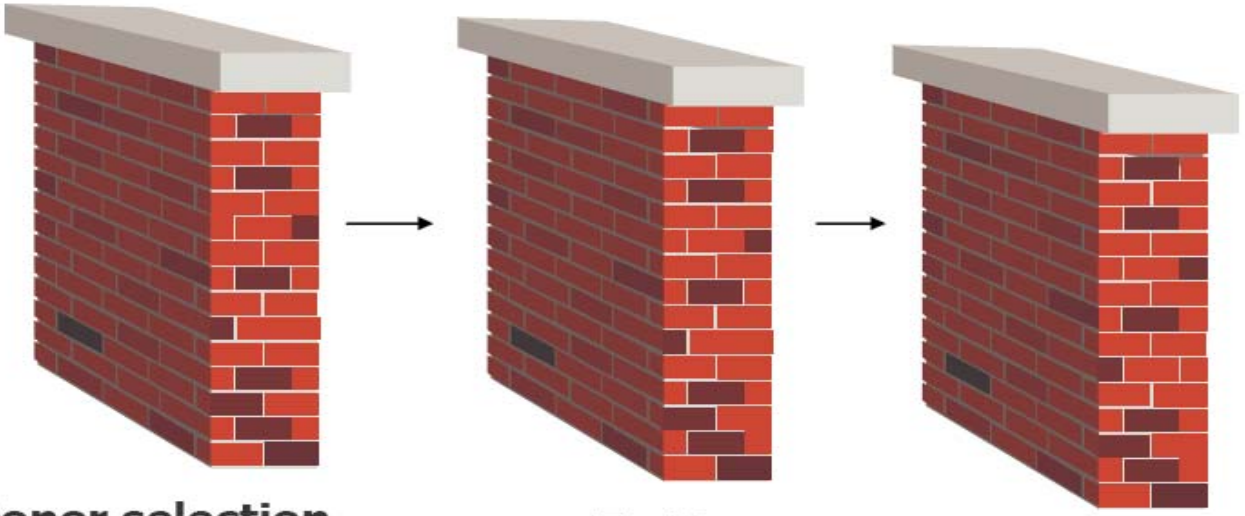
vCJD and haemophilia products
The Oz dimension

Albert Farrugia

vCJD & haemophilia products

- Blood is a vehicle for TSE transmission, and this gives rise to a risk for recipients of haemophilia concentrates
- The level of this risk can be assessed using parameters describing the manufacture and the exposure to these products
- These assessments and experimental findings predict a risk of cCJD for users; that epidemiological evidence currently negates this risk is reassuring for both cCJD and vCJD (but see later)
- The detailed specification of the donor pool to exclude individuals exposed to BSE can reduce risk; in blood economies dependant on pd FVIII this approach is limited by supply considerations
- Clearance of TSE agents is possible especially with highly purified products; such clearance needs to be validated but will decrease risk to insignificant levels

The road to SAFE hemophilia products
vCJD



Geographical deferrals

Test not available, under development

Processes can clear infective agent

WFH 2004

variant Creutzfeldt-Jakob disease and Hemophilia – Further guidance on assessing the risks of plasma-derived products for treating hemophilia

Prepared by Albert Farrugia, BSc, PhD, on behalf of the WFH Task Force on TSEs

Parameters in assessing the risk of TSE infection for an individual recipient of plasma derivatives:

- The number of pooled plasma donations
- The rate of TSE infection in blood donors
- The volume of the plasma donation
- The concentration of TSE infectivity in plasma
- The number of units of product from production process
- The amount of TSE clearance
- The amount of product to which the patient is exposed

Haemophilia products
Outcomes of risk assessments

- In terms of relative risk, the FDA, the TGA and the AFSSAPS assign FVIII concentrates the highest level amongst all the plasma derivatives
- Single FIX concentrates are of a significantly improved profile
- Absolute risks are judged very low by most authorities eg $<10^{-2}$ ID per year's treatment (FDA)
- However, this assumes a certain capacity for the manufacturing process to eliminate prions

Australian Risk Assessment 2002

Probability (P_u) that a single unit of product contains one or more infectious units:

$$P_u = \frac{n\, r\, v\, \lambda}{u\ \ f}$$

- n is the number of donations pooled
- r is the prevalence of vCJD infection
- v is the volume of a donation
- λ is the number of infectious units per mL
- u is the number of units produced
- f is the log-reduction in vCJD infectious units

Factor VIII: odds lifetime risk vCJD cases from exposure in one year

Infectious units per mL	Log reduction in infectivity	Per unit of product		Per treated patient		All Australia	
		Best estimate	95th centile	Best estimate	95th centile	Best estimate	95th centile
Exposure to vCJD based on UK mortality [38]							
1-100	4-log	1 in 62,000,000	1 in 7,700,000	1 in 310,000	1 in 38,000	1 in 350	1 in 44
1-100	5.4-log	1 in 1.6 billion	1 in 192,500,000	1 in 7,800,000	1 in 963,000	1 in 8,800	1 in 1,100
100-10,000	4-log	1 in 619,000	1 in 76,500	1 in 3,100	1 in 383	1 in 4	>1 in 2
100-10,000	5.4-log	1 in 15,500,000	1 in 1,900,000	1 in 77,700	1 in 9,600	1 in 88	1 in 11
Exposure to vCJD based on UK carriers [38]							
1-100	4-log	1 in 2,500,000	1 in 274,000	1 in 12,700	1 in 1,400	1 in 15	1 in 2
1-100	5.4-log	1 in 63,700,000	1 in 6,900,000	1 in 319,000	1 in 34,000	1 in 360	1 in 39
100-10,000	4-log	1 in 25,000	1 in 2,700	1 in 127	1 in 14	>1 in 2	>1 in 2
100-10,000	5.4-log	1 in 637,000	1 in 68,000	1 in 3,200	1 in 343	1 in 4	>1 in 2

Factor IX concentrate: odds lifetime risk vCJD cases from exposure in one year

Infectious units per mL	Log reduction in infectivity	Per unit of product		Per treated patient		All Australia	
		Best estimate	95th centile	Best estimate	95th centile	Best estimate	95th centile
Exposure to vCJD based on UK mortality [38]							
1-100	4-log	1 in 8,600,000	1 in 1,100,000	1 in 86,000	1 in 10,700	1 in 279	1 in 35
1-100	5.4-log	1 in 216,800,000	1 in 26,800,000	1 in 2,200,000	1 in 268,000	1 in 7,000	1 in 864
100-10,000	4-log	1 in 86,000	1 in 10,700	1 in 863	1 in 107	1 in 3	> 1 in 2
100-10,000	5.4-log	1 in 2,200,000	1 in 268,000	1 in 22,000	1 in 2,700	1 in 70	1 in 9
Exposure to vCJD based on UK carriers [38]							
1-100	4-log	1 in 353,000	1 in 38,000	1 in 3,500	1 in 381	1 in 12	> 1 in 2
1-100	5.4-log	1 in 8,900,000	1 in 955,000	1 in 89,000	1 in 9,600	1 in 286	1 in 31
100-10,000	4-log	1 in 3,500	1 in 382	1 in 36	1 in 4	> 1 in 2	> 1 in 2
100-10,000	5.4-log	1 in 89,000	1 in 9,600	1 in 888	1 in 96	1 in 3	> 1 in 2

French Risk Assessment Inputs 2000

- The smallest plasma pool necessary for fractionation
- The pool is infected by a single donation
- The extraction yield
- The cumulative reduction factor resulting from the manufacturing process
- The yearly total dose of product

French RA – Outcomes

Theoretical residual infectivity per recipient and per year.

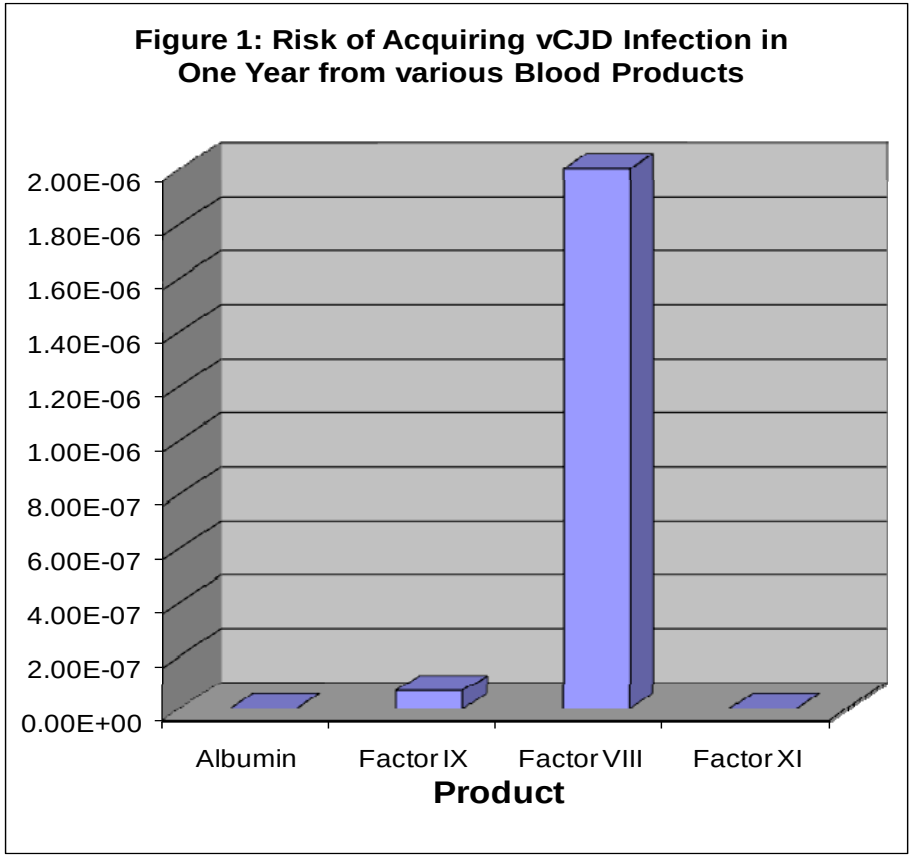
	Low Clearance	High Clearance
Factor VIII	2.4×10^{-2}	2.4×10^{-5}
Factor VII	1.5×10^{-3}	1.5×10^{-6}
Factor IX	7.2×10^{-7}	7.2×10^{-9}
Factor XI	3.5×10^{-5}	3.5×10^{-8}
Willebrand Factor	10×10^{-7}	10×10^{-8}
Fibrinogen	2×10^{-4}	2×10^{-5}
PPSB	1.9×10^{-5}	1.9×10^{-8}
Antithrombin III	2.7×10^{-3}	2.7×10^{-5}
Protein C	10×10^{-9}	10×10^{-9}
Albumin	7×10^{-5}	7×10^{-10}
Alpha 1 antitrypsine	4.4×10^{-6}	4.4×10^{-9}
Polyvalent Immunoglobulins	2.8×10^{-5}	2.8×10^{-10}
Anti Hobs IV immunoglobulins	1.5×10^{-5}	1.5×10^{-10}
Anti HBs IM immunoglobulins	9.5×10^{-10}	9.5×10^{-13}
Anti D immunoglobulins	1.5×10^{-7}	1.5×10^{-10}
Antitetanic immunoglobulins	9.5×10^{-10}	9.5×10^{-13}
Thrombin glue (no longer marketed)	5.4×10^{-6}	5.4×10^{-8}
Fibrin glue (no longer marketed)	5.5×10^{-2}	5.5×10^{-4}

PHAC RA 2005

A Cursory Analysis Addressing the Question of the Assessment of Exposure to Particular Batches of variant Creutzfeldt-Jakob Disease (vCJD) Implicated Factor XI Plasma Product.

Statistics and Risk Assessment Section
Blood Safety Surveillance and
Health Care Acquired Infections Division
Centre for Infectious Disease Prevention and Control
Public Health Agency of Canada

January 19, 2005



Estimating vCJD risk in factor concentrate

Australian TGA RA (Similar to all others)

Probability that a unit of medical product contains TSE infectious units is given by:

P = (d*r*v*i) / (u*l)

Where

d = number of blood / plasma donations pooled in production process

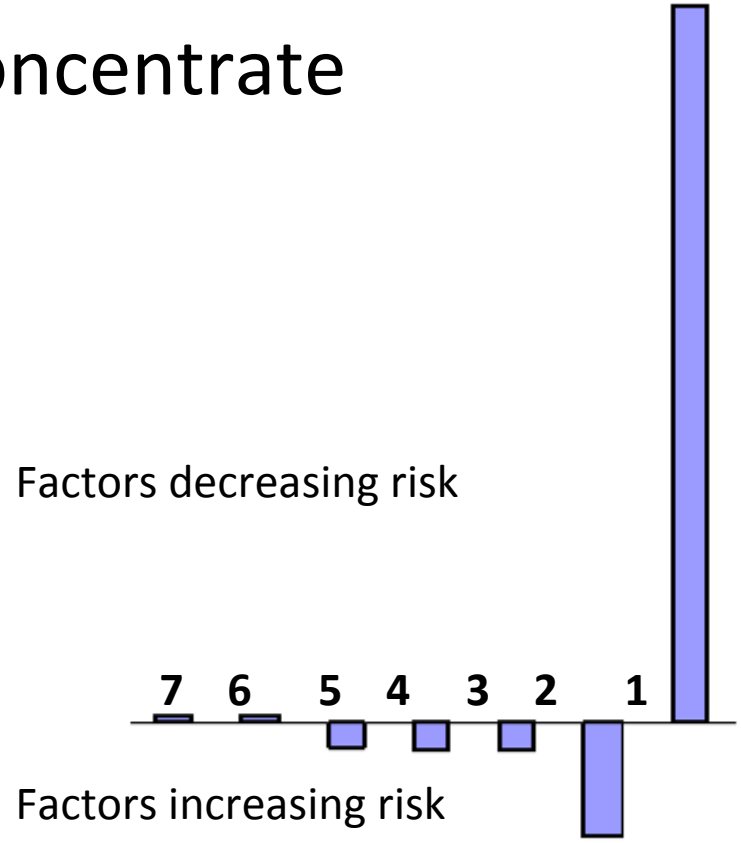
r = rate of TSE infection in Australia blood donors

v = volume of blood / plasma donation

i = number of infectious TSE units per ml plasma

u = number of units of product from production process

l = log reduction in number of TSE infectious units during production process



1 log manufacture reduction of vCJD agent
2 FVIII used per year (IU/Y,person
3 Prevalence of UK vCJD (cases/million)
4 efficiency of i.c vs i.v route
5 Infectivity in blood (ID50/ml)
6 Yield of FVIII from plasma (IU/L plasma)
7 Efficiency of donor deferral policy

S Anderson FDA

VCJD risk reduction and donor loss estimates
FDA/CDC Risk-weighted exposure day model

Policy	Risk reduction %	Donor loss %	Efficiency Risk reduction/donor loss
A	68	2.2	31
B	82	2.2	20
C	92	7.8-9.1	9.7-8.4
D	91	4.6-5.3	15.7-13.6

→ **Selection – deferral policies have modest results and will not affect significantly the potential of contaminating a plasma manufacturing pool**

TSE Clearance in FVIII concentrates
PPTA companies

Product	Step	MAB column	Q-Sepharose chromatography		Total
A	Log reduction(s), ID_{50}	4.6	3.5		8.1
	Step	3.5% PEG pptn	Heparin chromatography	Saline pptn + final filtrations	
A	Log reduction(s), ID_{50}	3.32	$\geq$3.45	2.28	$\geq$9.05
	Step	Subsequent pptn steps	Pptn+polishing+sterile filtration		
A	Log reduction(s), ID_{50}	3.5 – 3.9	2.9 – 4.0		6.4 – 7.9

WFH 2004

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- The volume of blood / plasma donation
- The concentration of TSE infectivity in plasma
- The number of units of product from the production process
- The amount of clearance of TSE infectious units achieved during the production process
- The amount of product to which the patient is exposed

Prevalence unknown, issue of sub clinical infection

Unknown

Varies between products

Health Protection Agency

Protecting people
Preventing harm
Preparing for threats

vCJD abnormal prion protein found in a patient with haemophilia at post mortem

- 70 years old PWH died of a condition unrelated to vCJD
- No symptoms of vCJD prior to his death
- vCJD abnormal prion protein identified during post mortem research tests
- New finding will not change the way patients with haemophilia are treated
- Final view as to how prion protein was transmitted has yet to be reached
- Investigations are continuing
- Patient had been treated with UK sourced clotting factors before 1999
- Patient's treatment had included one batch of Factor VIII that was manufactured using plasma from a donor who went on to develop symptoms of vCJD six months after donating the plasma in 1996

Dr Clive Dash, BPL Medical Director
Public Statement at IPPC March 09

The product recalled which was specified in the HPA statement regarding the person with hemophilia who was found to have vCJD prion on autopsy was the BPL concentrate 8Y

UK Risk Assessment vCJD in Blood Products
DNV 2003

"At BPL there are two production processes, yielding products of different purity:
Factor VIII Type 8Y - an intermediate purity product. …… for BPL's 8Y process a minimum of 1 log clearance is indicated……"

Vox Sanguinis (2009) 96 , 270

LETTER

A recipient of immunoglobulin from a donor who developed vCJD

•Female patient diagnosed with CVID at 61 yo
•Received IVIG with three weekly infusions of Vigam (BPL) from 1995 onwards.
• During January 1997 to February 1998 received batches of IVIG that contained plasma from a donor who later developed vCJD.
•The estimated ID50/g of these batches were 0·0000112 and 0·0000688, respectively.
•At age 72, she died of recurrence of adenocarinoma of the bowel.
•Post-mortem analysis of tissues :
•Western blotting of spleen and lymph nodes was negative for prion protein.
•No evidence of prion protein in the brain on histological, immunocytochemical or WB.
•Time interval between treatment with the implicated batches and death from unrelated causes was 9 years.

Although the patient received IVIG from a batch containing plasma from a donor who developed vCJD, the patient did not develop vCJD clinically, and there was no evidence of prion protein deposition using histopathological and molecular techniques.

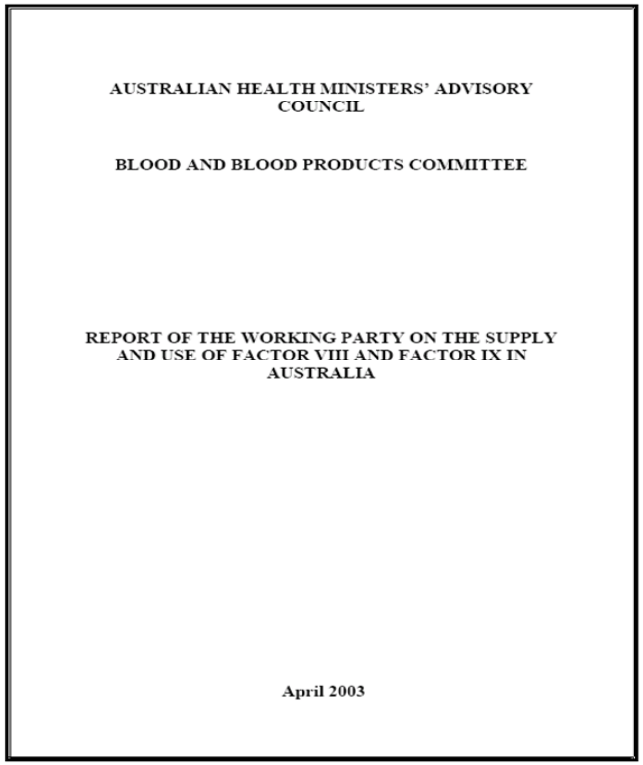
Prion Removal Factors

- Immunoglobulins
  - Cryoprecipitation: <1 [1], 1.0 [2], <1 - 2.4 [5]
  - Precipitation of fraction I: 1.1 [2], <1 – 3.1 [5]
  - Precipitation of fraction (I+)III: >3.3-3.8[9], 3.5[6], >3.7 [1], >4.0 [2], >4.3 [3], 5.3 [3]
  - PEG precipitation: >3.0[9]
  - Depth filtration: >2.8 [1], 2.8[6], 4.4[6], 6.4 [2,3], 6.0 [4]
  - Nanofiltration: 4.4[6]
- Ig: ≥ 3.0[7], ≥ 5.0-9.4[8], ≥6.5 [1], ≥ 6.3-6.8[9], ≥6.4 [2&3], 7.9 [4]

Foster et al., Vox. Sang. [2000] 78: 86
Lee et al., Transfusion [2001] 41: 449
Vey et al., Biologicals [2002] 30: 187
Biotest, internal report.
Baxter, internal report.

[2] Lee et al., J Virol Meth [2000] 84: 77
[4] Rohwer / Baxter & ARC, preliminary results
[6] ZLB, internal report.
[8] Aventis Behring, internal report.

Key events



AUSTRALIAN HEALTH MINISTERS' ADVISORY COUNCIL

BLOOD AND BLOOD PRODUCTS COMMITTEE

REPORT OF THE WORKING PARTY ON THE SUPPLY AND USE OF FACTOR VIII AND FACTOR IX IN AUSTRALIA

April 2003

http://www.nba.gov.au/pdf/factor_VIII_IX.pdf

P 57

Special Expert Committee on Transmissible Spongiform Encephalopathies
June 2002

" ***Although the theoretical risks from plasma-derived AHF are very small, they cannot be said to totally negligible. It is prudent to recommend that, as soon as feasible, AHF be made available in recombinant form, or as a product of a purification process that is proven to reduce prion content by at least 7 logs.***"

Media Release

The Hon Tony Abbott MHR
Minister for Health and Ageing

30 August 2004 ABB140/04

GOVERNMENT RESPONSE TO THE SENATE INQUIRY INTO HEPATITIS C AND THE BLOOD SUPPLY

"……..The Government has agreed to fund access to recombinant clotting factors for haemophilia patients. A small number will not be able to use recombinant products and will continue to be provided with plasma-derived clotting factors. The Government will provide ongoing funding of $80.7 million over four years, to be supplemented by the States and Territories……"

vCJD protection measures

- ***Risk Assessment from SECTSE (now TSEAC)***
- ***Risk from Biosate very small but not totally negligible***
- ***TGA-ARCBS-CSL agreement re donor selection***

vCJD protection measures

- ***Recombinant funding resulted in more flexibility***
- ***New precautionary measure introduced 05-06***
- ***Only donors not ever leaving Australia or NZ eligible for donating for Biostate***

Australian Risk Assessment 2002

Probability (P_u) that a single unit of product contains one or more infectious units:

$$P_u = \frac{n\, r\, v\, \lambda}{u\ f}$$

Pμ is 0 if r and λ are 0:
This can only be approached
when there is no exposure to BSE

- *n* is the number of donations pooled
- *r* is the prevalence of vCJD infection
- *v* is the volume of a donation
- *λ* is the number of infectious units per mL
- *u* is the number of units produced
- *f* is the log-reduction in vCJD infectious units

Measures to enhance safety of Biostate

- SECTSE's RA identified FVIII recipients as at highest relative risk
- This risk comes primarily from the life-long use of these products, and the difficulty in clearing prions from FVIII manufacture
- Therefore, TGA, CSL and the ARCBS negotiated measures which would achieve an acceptable risk profile through other inputs in the RA
  - From 1/1/06 – all plasma for Biostate from OZ/NZ donors only
  - From 1/4/06 – all Biostate on the market from such plasma

Recent developments

- In mid 2007, the TGA lifted the restrictions applying to donors for Biostate.
- These restrictions are now identical to those for all other plasma products on the Australian market
- Public information related to this event may be extracted from the ISTH presentation *"Addition of Prion Reduction Factors from Single Step Experiments may overestimate Manufacturing Process Clearance Capability"* by W. Schaefer, H. Pham, T. Martinelli, and A. Groener

CSL poster at XXI ISTH Congress, July 6 - 12, 2007, Geneva, Switzerland

	Prion reduction factor [log_{10}]			
Manufacturing step	Single manufacturing steps		Combined manufacturing steps	
	Microsomes	purified PrP^{Sc}	Microsomes	purified PrP^{Sc}
$Al(OH)_3$ adsorption / heparin precipitation	0.8	1.8	1.1	2.5
Glycine /NaCl precipitation & charged depth filtration (30ZA/VR07)	2.9	3.3	1.2	1.3
SD treatment / Gelfiltration	1.1	n.d	0.3	- 0.3
EKV/DVD filtration	≥ 3.0	≥ 3.9	1.4	1.4
Overall Prion Reduction Factor	**≥ 7.8**	**≥ 9.0**	**4.0**	**4.9**

AF to Gavin Finkelstein 20 December 2006

Mr Gavin Finkelstein
President
Haemophilia Foundation of Australia

[transmitted by email]

Dear Mr Finkelstein

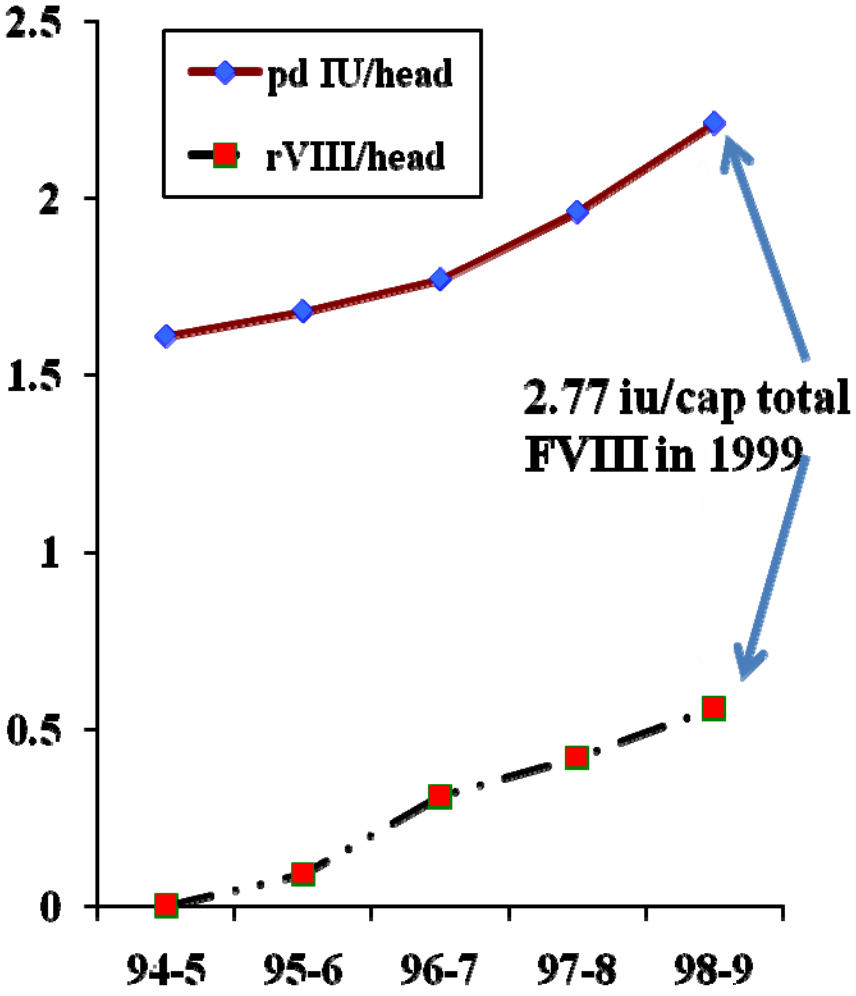
Thank you for your letter dated 20 December 2006 conveyed to me by Ms Sharon Caris.

I appreciate the sensitivity you have expressed regarding matters which are commercial-in-confidence. While you will understand that the TGA has to observe such sensitivities, I can assure that the safety of the haemophilia community, and that of all blood product recipients in Australia, is ever in the minds of this Administration. I believe the HFA is aware of the role of the TGA in transitioning the state of care for haemophilia from intermediate to high purity plasma to recombinant products over the course of the past five years.

This has brought the level of safety of products for patients with haemophilia to be reflective of international best practice. You may be assured that this will continue to be the case.

Safety and Supply of haemophilia therapies

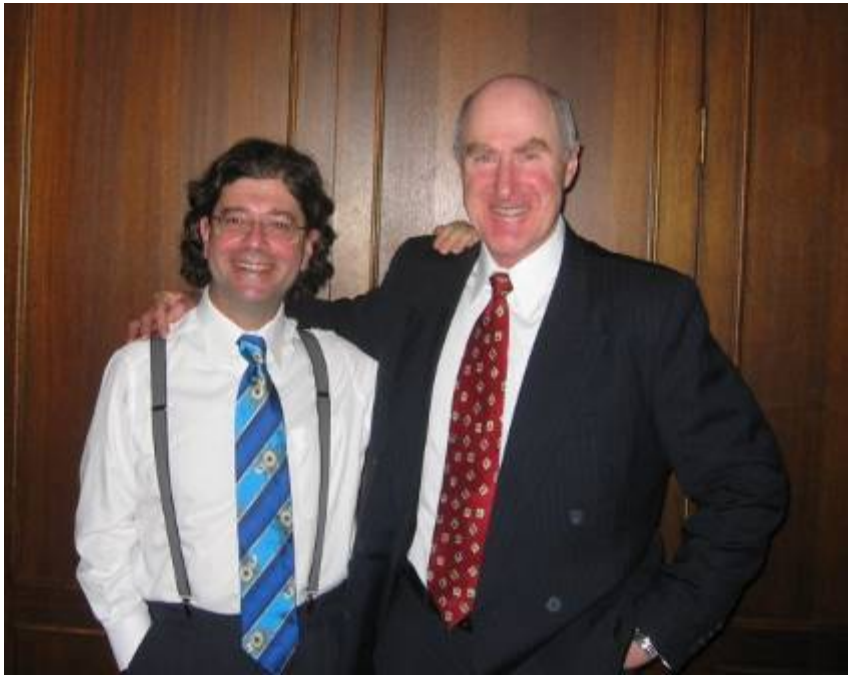
A decade of achievement



- Over the past ten years, haemophilia therapies in Australia have progressed from single viral inactivated to double viral inactivated to recombinant therapies produced on dedicated equipment
- Over the same period, the amount of FVIII available for treatment has more than doubled
- Products for specific treatment of VWD and bleeding in multiple disorders have also been approved
- Access is still influenced by complex reimbursement systems
- These achievements have involved many stakeholders, including the product regulator

"All these things were done…….
and they were wonderful to behold"

Charlie Wilson's War



"I recall a bigger brighter world
a world of books
and silent times in thought……"

McLennan 1983