

Product regulation in the Australian haemophilia environment

A question of balance

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TGA

(Willie) Murphy's Law(s) of blood safety

ANZSBT Christchurch 2003 & Pathophysiol Haemost Thromb 2002;32(suppl 1):1-4

- **Safety is control of risk, not avoidance of risk**
 - **Because you can do the former, not the latter**
- **Patients may be better safeguarded now than they were fifteen years ago**
 - **(would they agree? Do they think that the blood industry achieved that of it's own free will?)**
- **But the environment in which blood is collected is just as unsafe as it ever was**
 - **and no amount of inactivation or testing will change that.**

Good turning bad

Examples of blood safety measures having deleterious outcomes (challengeable)

- **HCV antibody testing**
- **Heat treatment of FVIII**
- **Plasma depletion of RCCs**
- **Use of RCCs rather than WB**
- **HCV transmission with IVIG**
- **Development of FVIII antibodies**
- ***Y.enterocolitica* infections**
- **Association with increase in maternal deaths from haemorrhage**

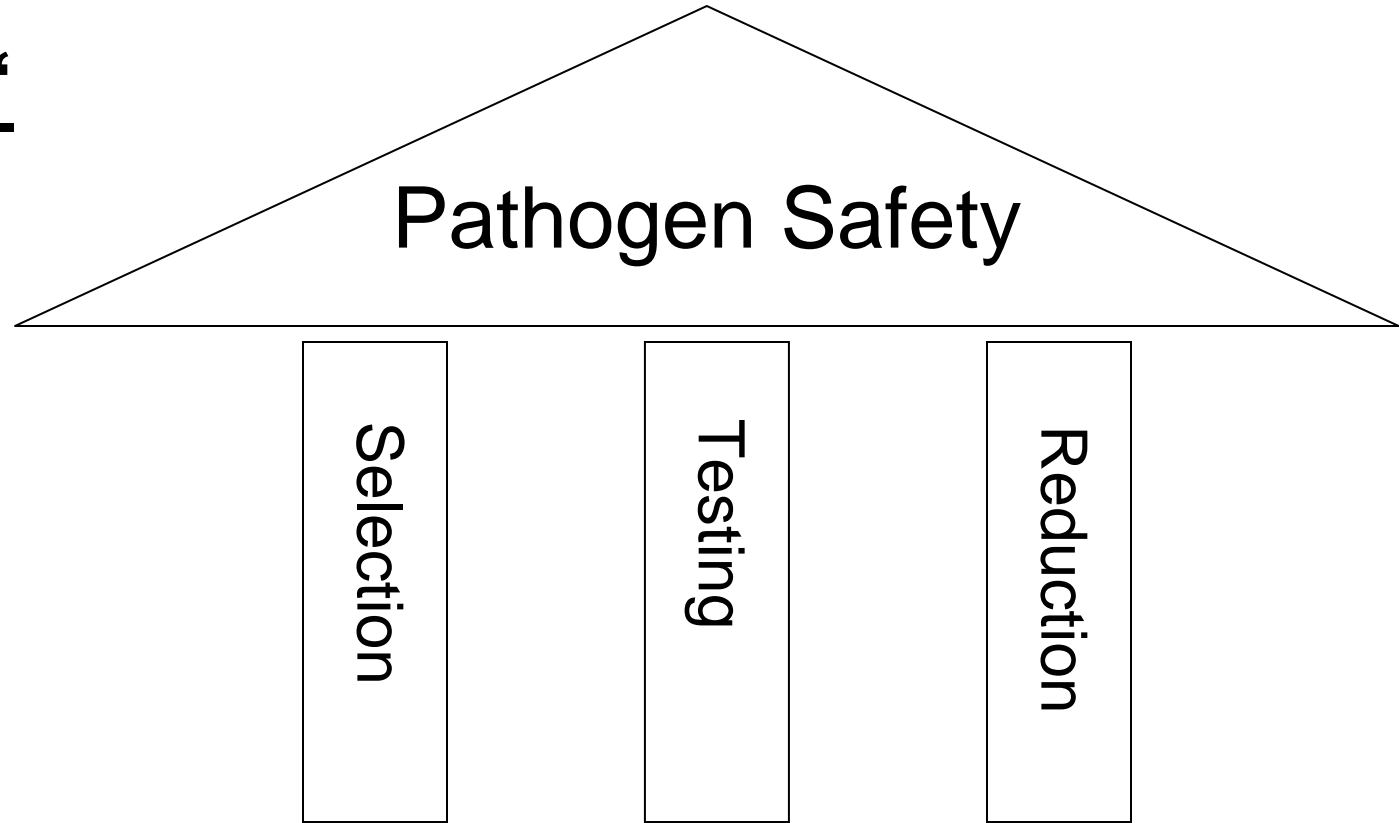
The chronic recipients of plasma derivatives are exposed to the whole of the blood supply.

This can happen in time frames which are not covered through current surveillance mechanisms.

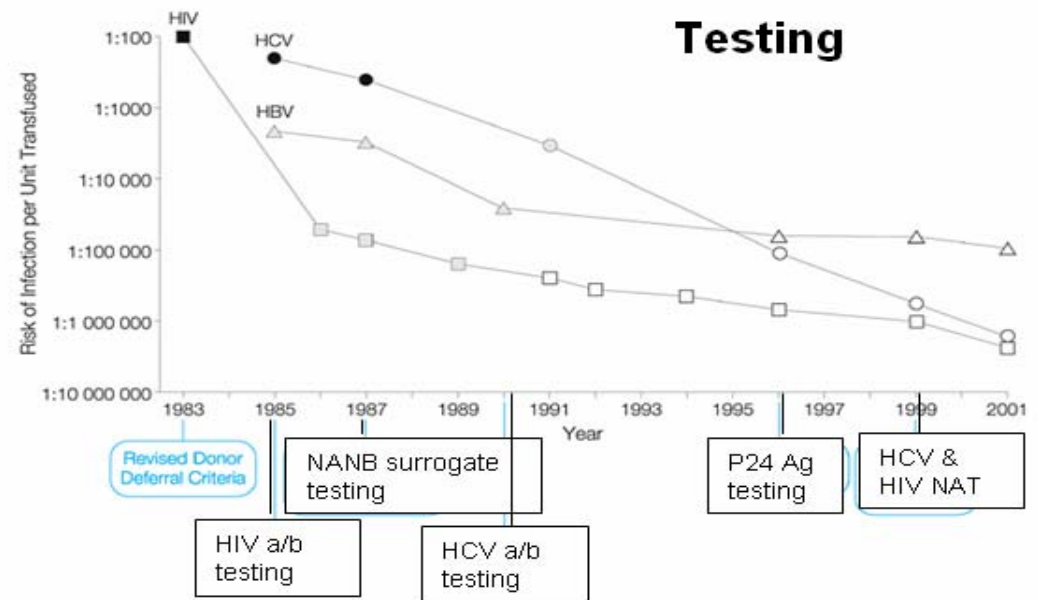
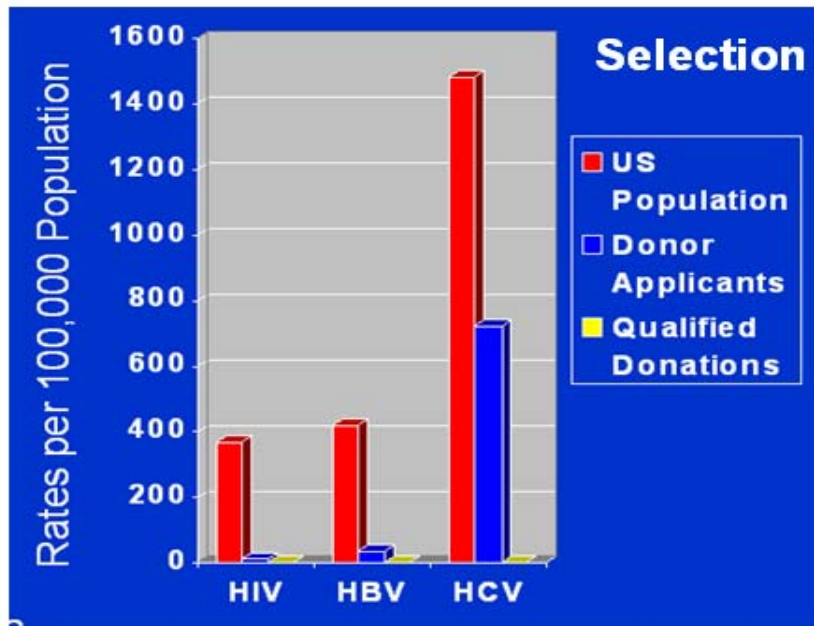
Therefore, the possible exposure of these patients to new pathogens requires constant recognition

“Safety tripod”

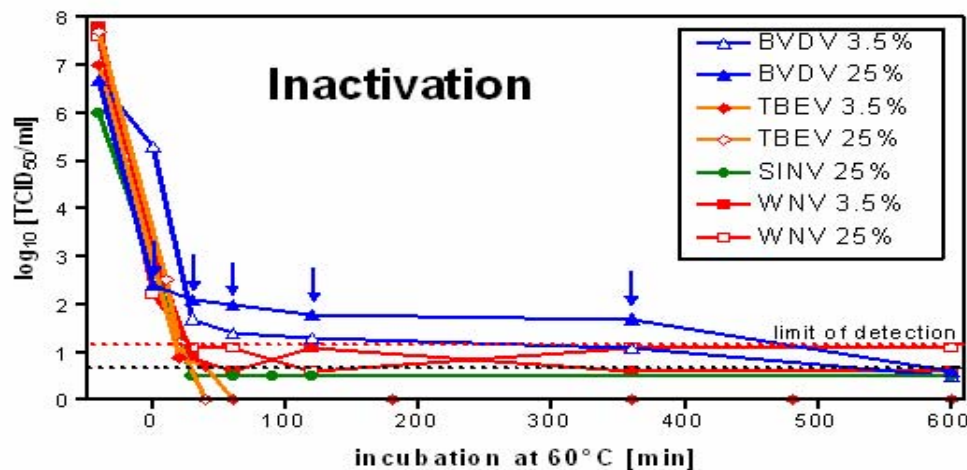
- Selection
- Testing
- Reduction



Contributions of the different parts of the safety tripod

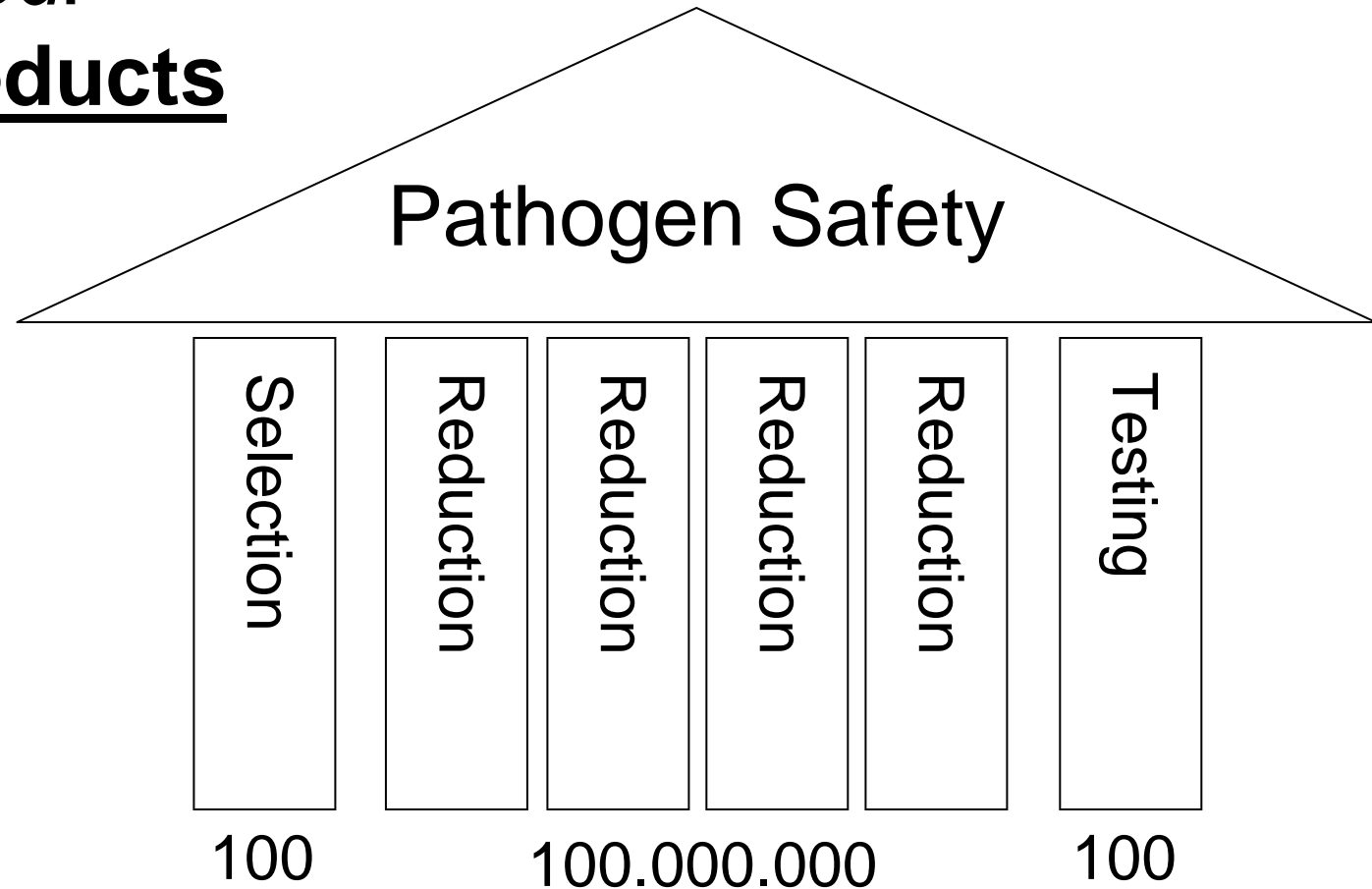


Pasteurization of Human Albumin



- Donor selection removes app 1 log of potential viral burden
- Testing removes 1 – 2 logs
- Viral inactivation is required to remove > 6 logs and generally exceeds this
- VI is non specific to viral type – WNV example

The *safety tripod*:
for **plasma products**

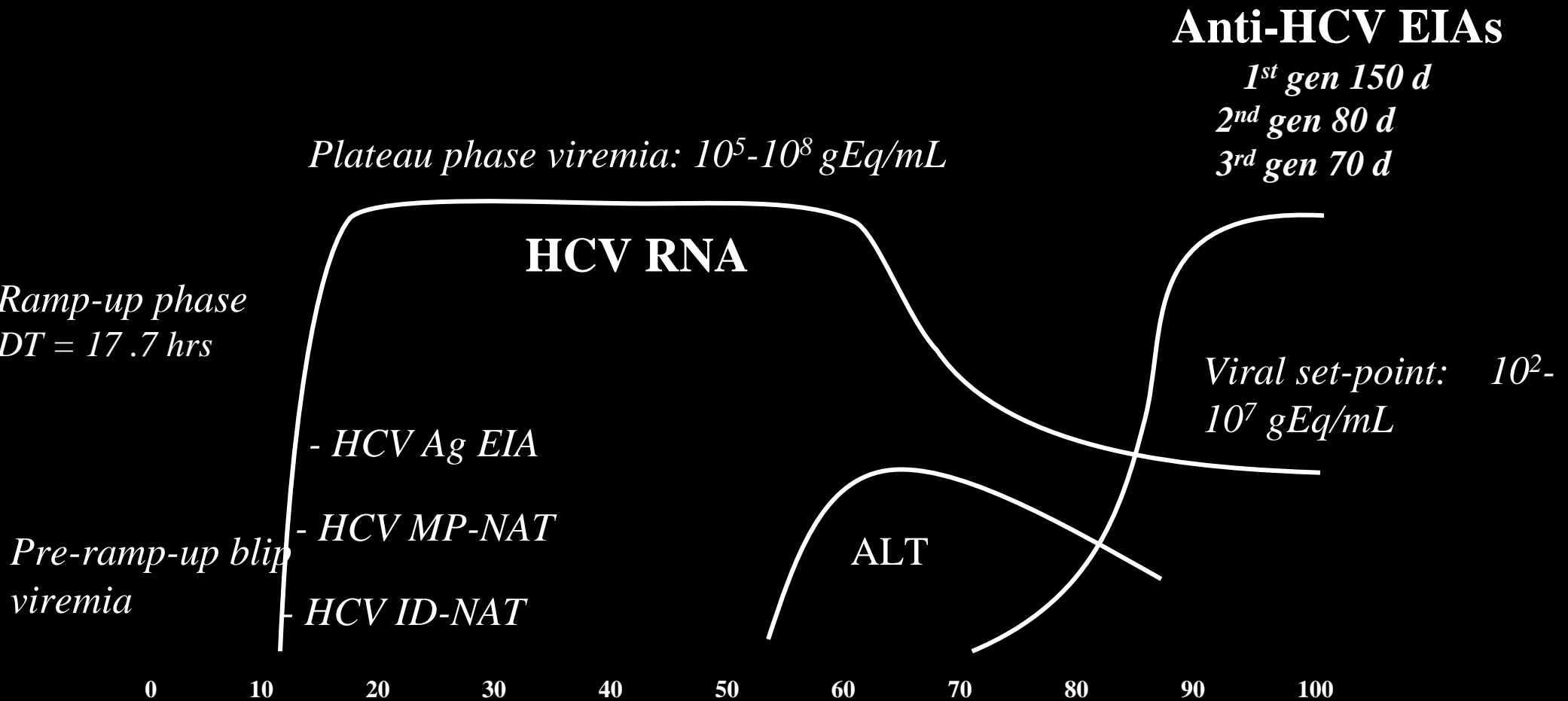


→ **REDUCTION** is clearly the most significant !

Progression of pathogen safety measures for haemophilia products

- The safety of pooled plasma derivatives has followed a different path to that for blood transfusions
- Blood transfusions are very safe because of donor selection measures and sensitive screening tests
- Until, arguably, very recently, these measures could not ensure the safety of plasma derivatives
- Equally arguably, some of these measures could *decrease* the safety of plasma derivatives eg
 - Removal of HBc Ab +ve donations could also remove HBsAg Ab +ve donations – effect on anti-HBV IgG
 - Removal of HCV Ab +ve donations led to more free HCV in the plasma pool which partitioned into product during fractionation

HCV markers during early infection



Prevalence of HCV antibody in Australia

HCV Projections Working Group 2006

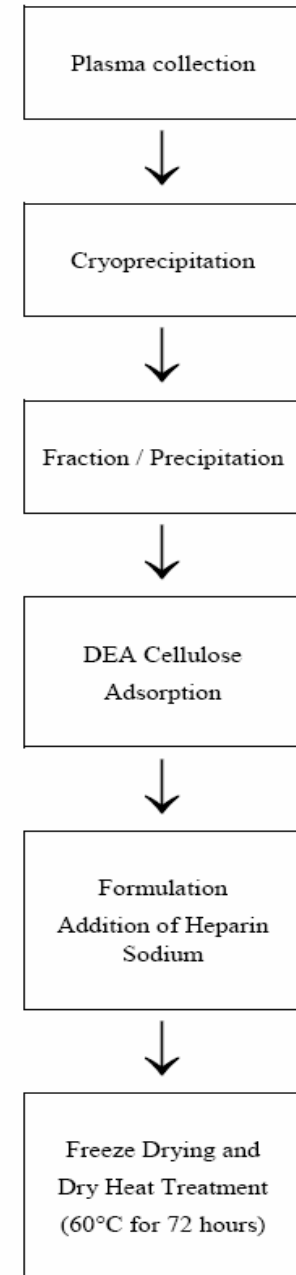
Site	Year	Prevalence
WA	1987-89	0.7% (350/50K)
NSW	1987-89	0.8% (400/50K)
Geelong	1990	0.4% (200/50K)
Sydney	1990-91	0.4% (200/50K)
Victoria	1990-97	1.0% (500/50K)
Brisbane	1994-95	0.5% (250/50K)

REPORT OF THE
EXPERT ADVISORY GROUP ON HEPATITIS C
AND PLASMA IN 1990

May 2003

“The plasma in question was not to be used for the manufacture of Prothrombinex as it was manufactured by a process of heating to 60°C. There was a possibility that viruses that were not destroyed at that temperature could be transmitted.”

Flow chart for the manufacture of Prothrombinex



Agent prevalence and manufacturing scale on risk of exposure

Lynch et al 1996

No of donors	No of independent infusions					
	1		10		100	
	Prevalence		Prevalence		Prevalence	
	1/500K	1/50K	1/500K	1/50K	1/500K	1/50K
60 K	11%	70%	70%	100%	100%	100%
25 K	5%	39%	39%	99%	99%	100%
10 K	2%	18%	18%	86%	86%	100%
2.5 K	0.5%	5%	5%	39%	39%	99%
0.6 K	0.1%	1%	1%	11%	11%	70%
0.1 K	0.02%	2%	0.2%	2%	2%	18%

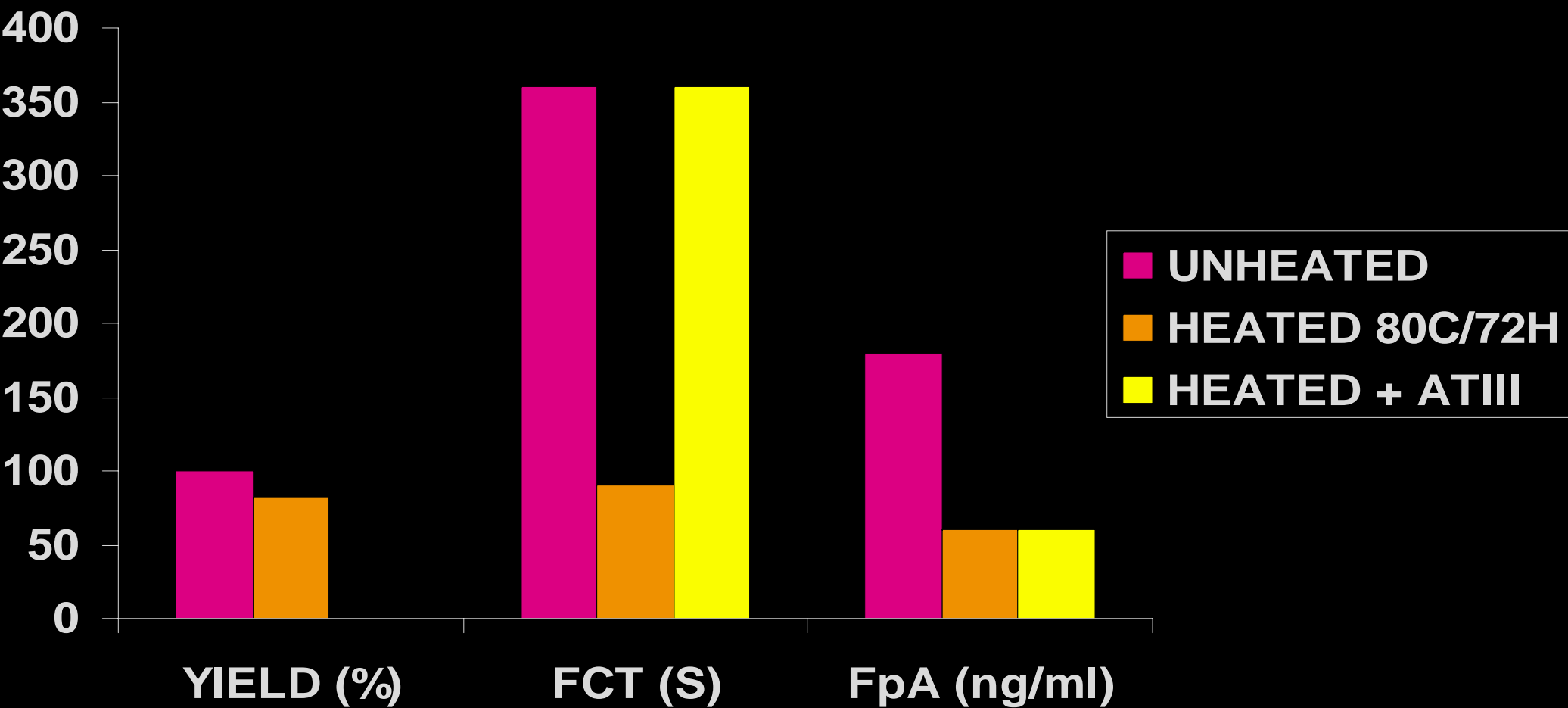
Progression of FIX products in Australia

- 1970's - 1984 - PCC
- 1984 - 1992 - PCC - 1st generation VI (HIV)

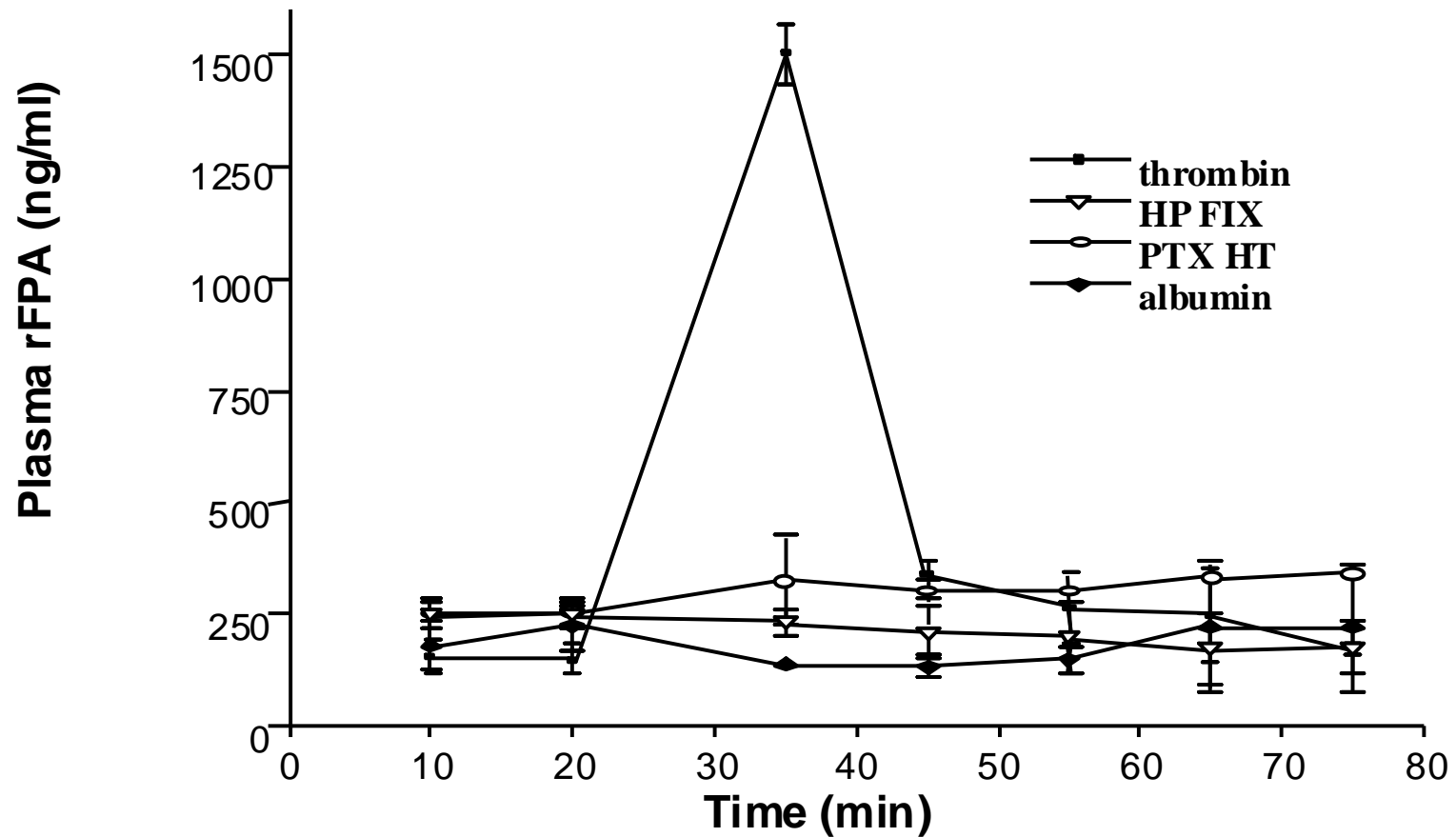
[between these two eras, the first HCV Ab test was introduced. This test was insufficiently sensitive to decrease the HCV load in plasma pools to a level which would protect chronic recipients. The presence or absence of Ab +ve units would not affect this situation; in fact, US data suggest that the test may have *increased* the HCV load in cryosupernatant (starting material of PCC manufacture)]

- 1992 - 1998 - PCC - 2nd generation VI (HCV)
- 1998 - Single Factor FIX - 3rd generation VI (2 steps) (non-enveloped viruses, prions)
- 2000 - recombinant FIX
- 2005 – (PCC – 3rd generation VI – 2 steps)

Prothrombin Complex Concentrate Thrombogenicity risks

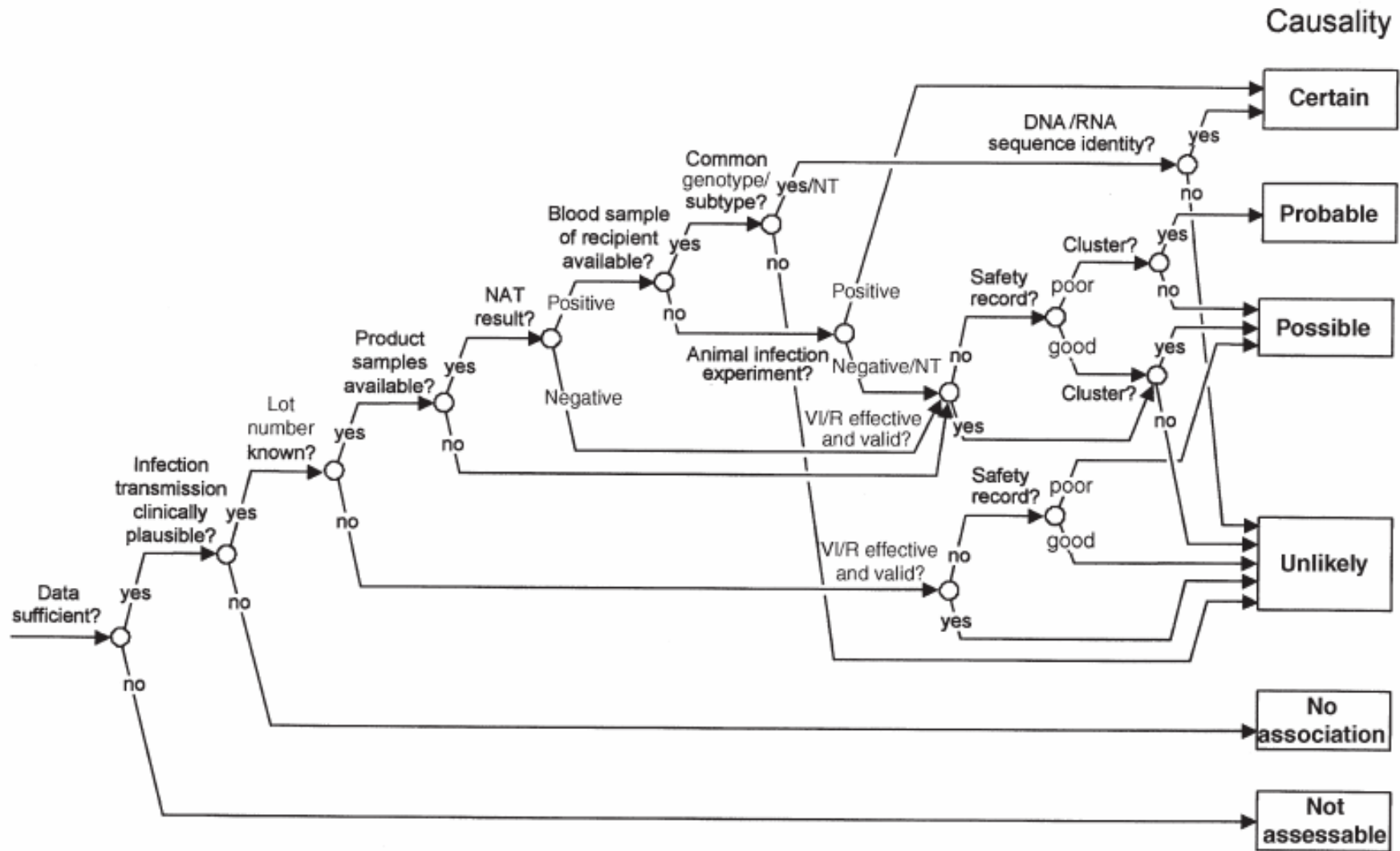


Effect of infusion of PTX-HT and HP FIX on plasma rFPA concentration



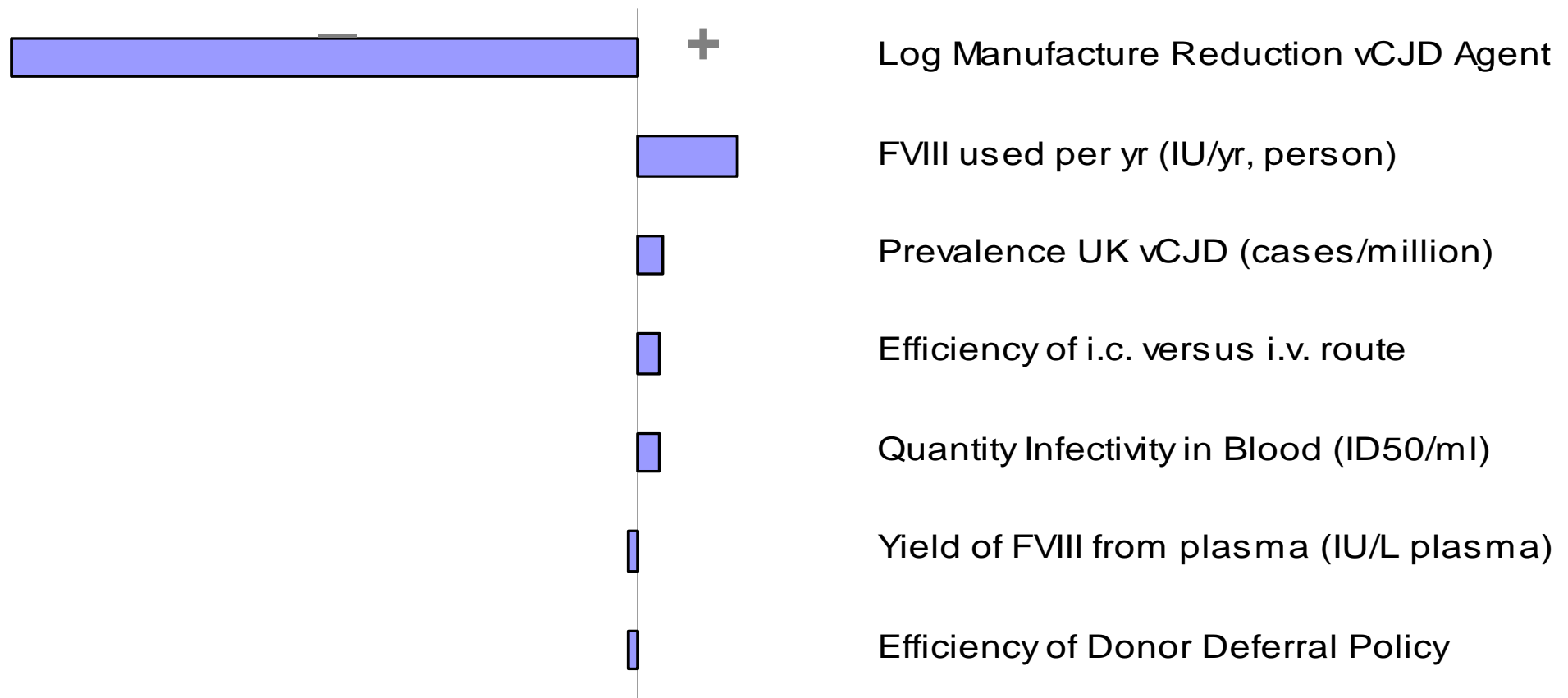
Causality assessment of suspected virus transmission by human plasma products

TRANSFUSION 2001;41:1020-1029.



Importance Analysis for vCJD risk Anderson 2006

Importance Analysis ranking influential factors for predicted vCJD exposure (yr) using prevalence estimates from 0.7 to 700 cases per million



Prion Clearance Capacity

Product	Process Step(s)	_____LRF
Albumex/Intragam-P	delipidation	≥ 2.40
Albumex	chromatography	≥ 5.58
Intragam P	chromatography	≥ 5.41
IMIG	Cohn	≥ 5.63
MonoFIX VF	35N + 15N nanofilter	5.32
Thrombotrol	15N + 15N nanofilter	≥ 5.65
PTX HT	chromatography	1.44*
Biostate FVIII	Prec / chrom	0.51- 1.52^ 1.8 - 3.1

* *Nanofiltration is being added to PTX HT*

^ *Additional donor restrictions in place for Biostate. R&D investigation for introduction of nanofilters*



Review of
Australia's Plasma
Fractionation Arrangements



PHILIP FLOOD AO
PETER WILLS AC
SIR PETER LAWLER OBE
GRAEME RYAN AC
KEVIN A. RICKARD AM

“.....a risk assessment conducted by the Special Expert Committee on Transmissible Spongiform Encephalopathies (SECTSE) of the National Health and Medical Research Council (NHMRC) has found that although the theoretical risks of transmission of [variant Creutzfeldt-Jakob disease] are very small for Biostate with the current manufacturing process, these risks cannot be said to be totally negligible. Therefore it has been agreed that further precautions should be taken to reduce the already small risk as soon as practicable. As a result the TGA, the Australian Red Cross Blood Service (ARCBS) and CSL Limited have agreed to introduce a staged series of targeted donor selection processes for Biostate manufacture.”



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“Following the increased access to government-funded recombinant Factor VIII and the consequent reduction in demand for Biostate, it was possible to introduce a new precautionary measure to further reduce the theoretical risk. A plasma collection policy was introduced in June 2005 and came into full effect after 1 April 2006 to ensure that plasma used in the production of Biostate was sourced from donors who had not lived or travelled outside Australia and New Zealand since 1980.²⁹ Such donors have an extremely low risk of being exposed to vCJD because there have been no confirmed cases of BSE or vCJD in either country. Through this measure an additional level of protection against the theoretical risk of prion transmission is available to protect people who receive Biostate.”



**Review of
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“TSEAC’s requirements for prion clearance guide the TGA in its approval of plasma products, whereby an overseas product has been approved which has a prion clearance reflective of TSEAC’s advice”

Risk assessment as a regulatory tool

SECTSE 18 March 2005

..... Through using a global risk model which draws inputs, including prevalence, blood titre and clearance, into a final assessment for each product.....decisions regarding putting and retaining products on the market may be made taking into account the particular features of each product source and manufacturing method. This may allow usage of products sourced from a different BSE status than Australia's as long as other factors, primarily prion clearance, result in a risk profile equal or superior to that of the domestically sourced products.

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

TGA's report card 2007

Since I spoke to you last, we have

- Approved new products for haemophilia A & VWD
- Approved variations enhancing the safety of haemophilia A, VWD and other coagulation products
- Approved new generations of recombinant products

Products sourced from overseas

- Up to 2004, the TGA would not accept for review any overseas-sourced blood product **unless it was superior to the domestic equivalent.**
- Several overseas sourced products were registered during the period of implementation of this measure
- These included products not manufactured in Australia, such as fibrin sealant, Protein C concentrate, virally inactivated plasma etc
- In addition, products considered by the TGA to show superiority over the domestic product were also accepted for review and, after evaluation, registered
- These included the overseas IVIGs – Sandoglobulin, Intraglobin-F (subsequently withdrawn by the sponsor due to lack of a market) and Octagam, the anti-D WinRho etc



Australian Government

**Department of Health and Ageing
Therapeutic Goods Administration**

All overseas derived products approved for the Australian market by the TGA have a prion (and viral) safety profile which is at least equivalent to that of the Australian product

- **Plasma derivatives are amongst the most highly regulated therapeutic goods**
- **Regulatory and industry measures has led to a high level of safety in plasma derivatives marketed in the developed world**
- **These measures are all in place for the plasma products marketed in Australia, irrespective of their source**
- **Issues of safety and efficacy of plasma products will continue to engage the regulator**

Acknowledgments

- Slides from innumerable colleagues
- The improvements in the safety of the Australian blood supply outlined in this talk were possible through the close and collegial relationship between the NBA and the TGA. I want to recognise Alison Turner's leadership and courage in introducing supply arrangements for the Australian blood system.

Line Robillard 1943 - 2006

This talk is dedicated to the memory of my friend, comrade and mentor who passed nearly a year ago. Her leadership and service to the world community of people with haemophilia will serve as an example for many years to come

