Science and the Regulation of Biologics: From a Rich History to a Challenging Future

Bethesda, 23/24 September 2002

International Biologics Issues

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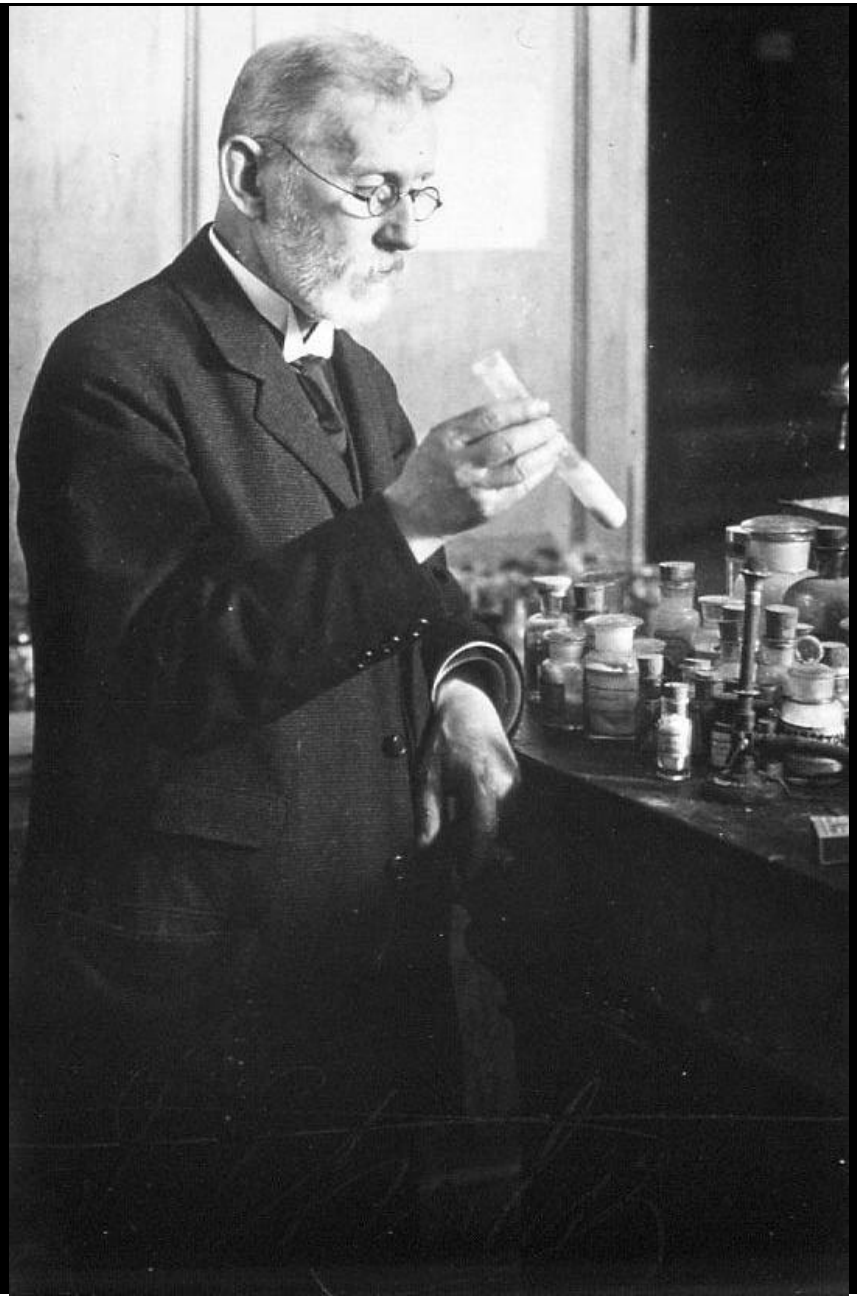
PEI



Paul Ehrlich

Die Wertbemessung des Diphtherieheilserums
und deren theoretische Grundlagen

Klinisches Jahrbuch 6, 299-326, 1897

PEI

Potency of Anti-D Immunoglobulin

Specification: ≥990 IU/ml

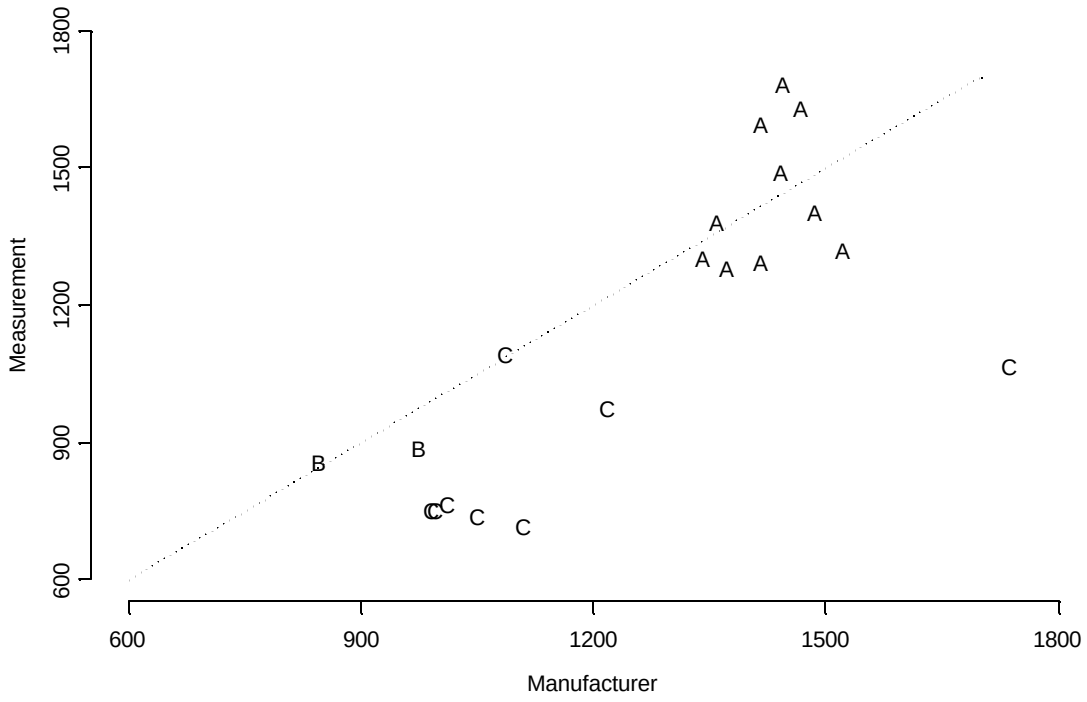
Ch.-No.	MAH	PEI (Flow cytometry)	Ext. Laboratory (EIA)	Ext. Laboratory (Autoanalyzer)
180102C	1172	699	--	--
180402C	995	791 769	872	787
180502C	1110	768 762	813	764
Positive control	--	1321	--	1255

All Results in IU/ml

PEI

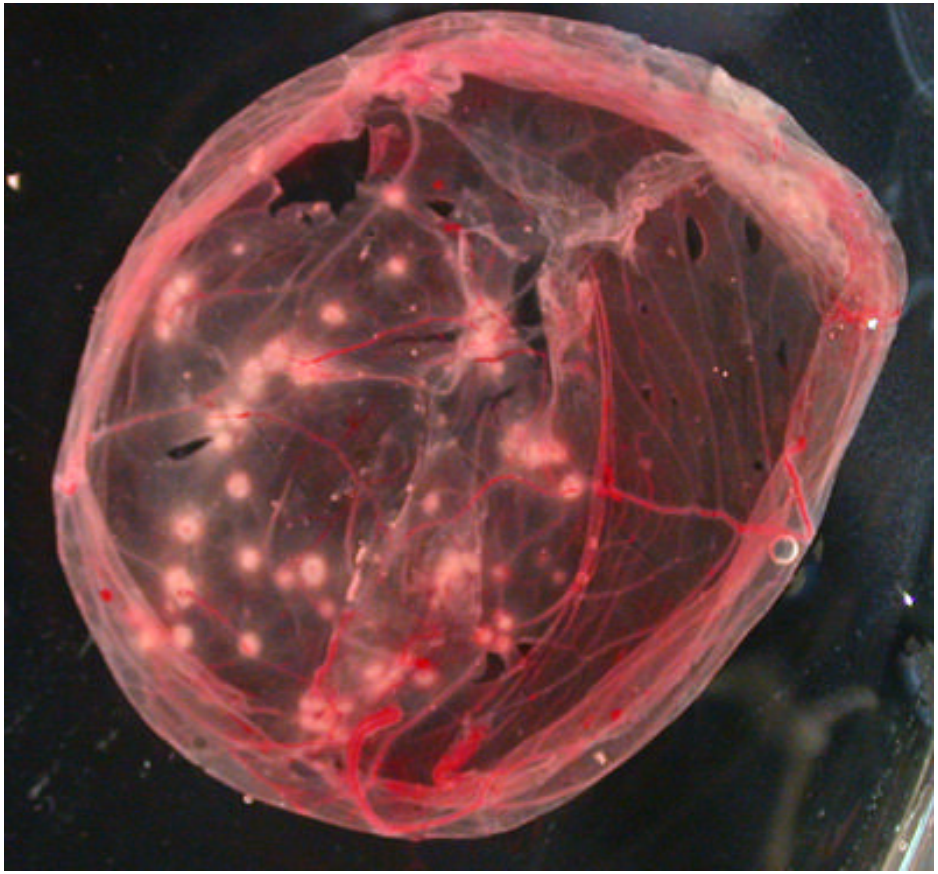
Poteny of Anti-D Immunoglobulin

Correlation between PEI's and Manufacturer's Results



PEI

Smallpox Vaccine Infected CAM



52 pock forming units (p.f.u.) visible

Dilution: 2×10^6

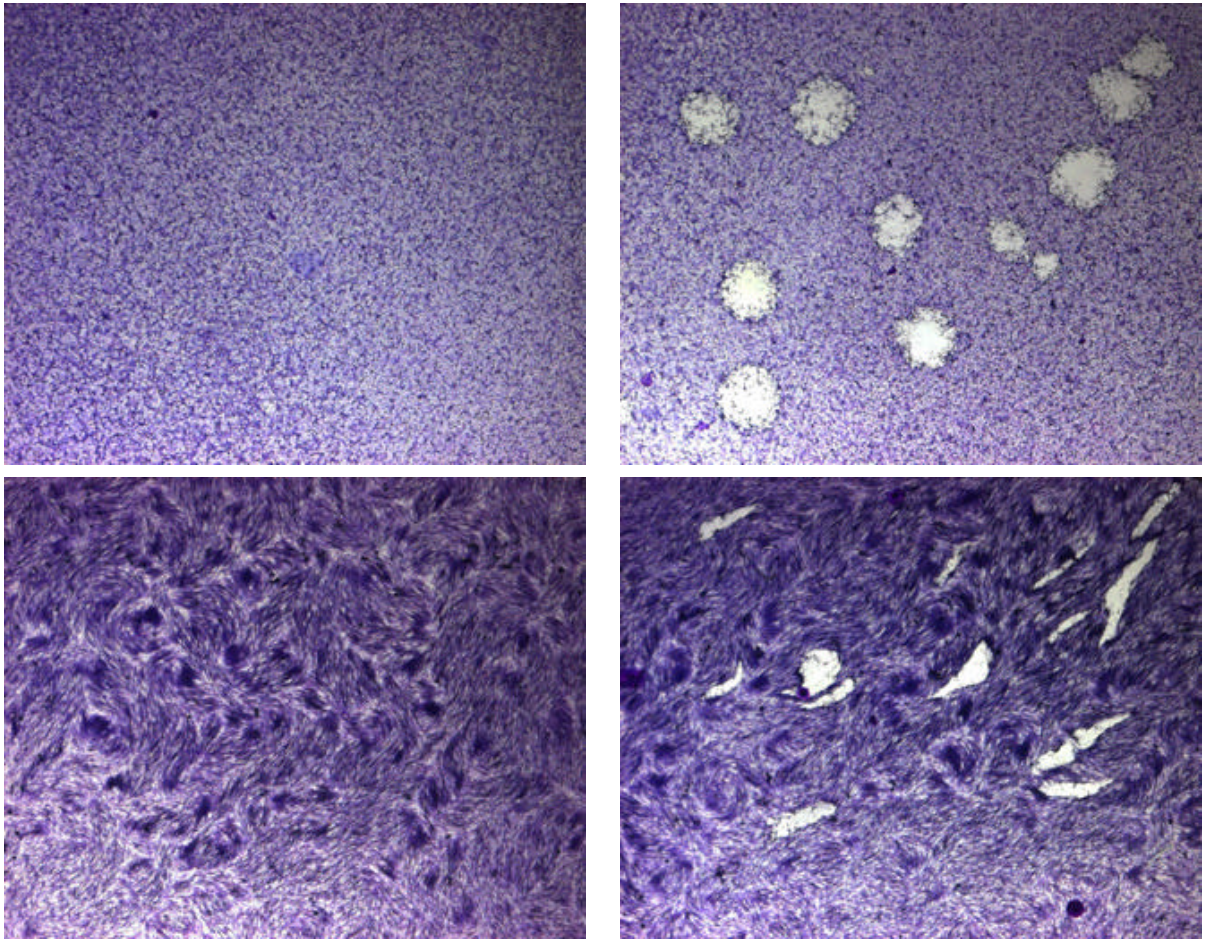
Potency: $1{,}04 \times 10^8$ p.f.u./ ml

PEI

Vaccinia Virus Plaque Formation in Cell Culture

mock

Vaccinia Virus



VERO cells

HeLa cells

PEI

Comparison of Potency

Vaccine titers analysed on CAM and in cell culture

Company	Batch No	Titer p.f.u./ml CAM	Titer p.f.u./ml CAM	Titer p.f.u./ml
		Manufacturer	PEI	VERO
Berna Biotech	13449	$1,9 \times 10^8$	$2,7 \times 10^8$	$2,3 \times 10^7$
Berna Biotech	13450	$1,9 \times 10^8$	$1,1 \times 10^8$	$6,2 \times 10^7$
Berna Biotech	13451	$1,8 \times 10^8$	$1,6 \times 10^8$	$5,0 \times 10^7$
		Manufacturer	PEI	HeLa
Bayer. Landesimpfanstalt	5/78 EG 859 EG	$2,0 \times 10^7$	$8,8 \times 10^7$	$2,2 \times 10^8$
Bayer. Landesimpfanstalt	5/80 EG	$9,5 \times 10^5$	$9,4 \times 10^7$	$7,4 \times 10^7$
Bayer. Landesimpfanstalt	2,3/80 EG	$4,5 \times 10^6$	$8,5 \times 10^7$	$1,1 \times 10^7$

PEI

International Biologics Issues

- Potency

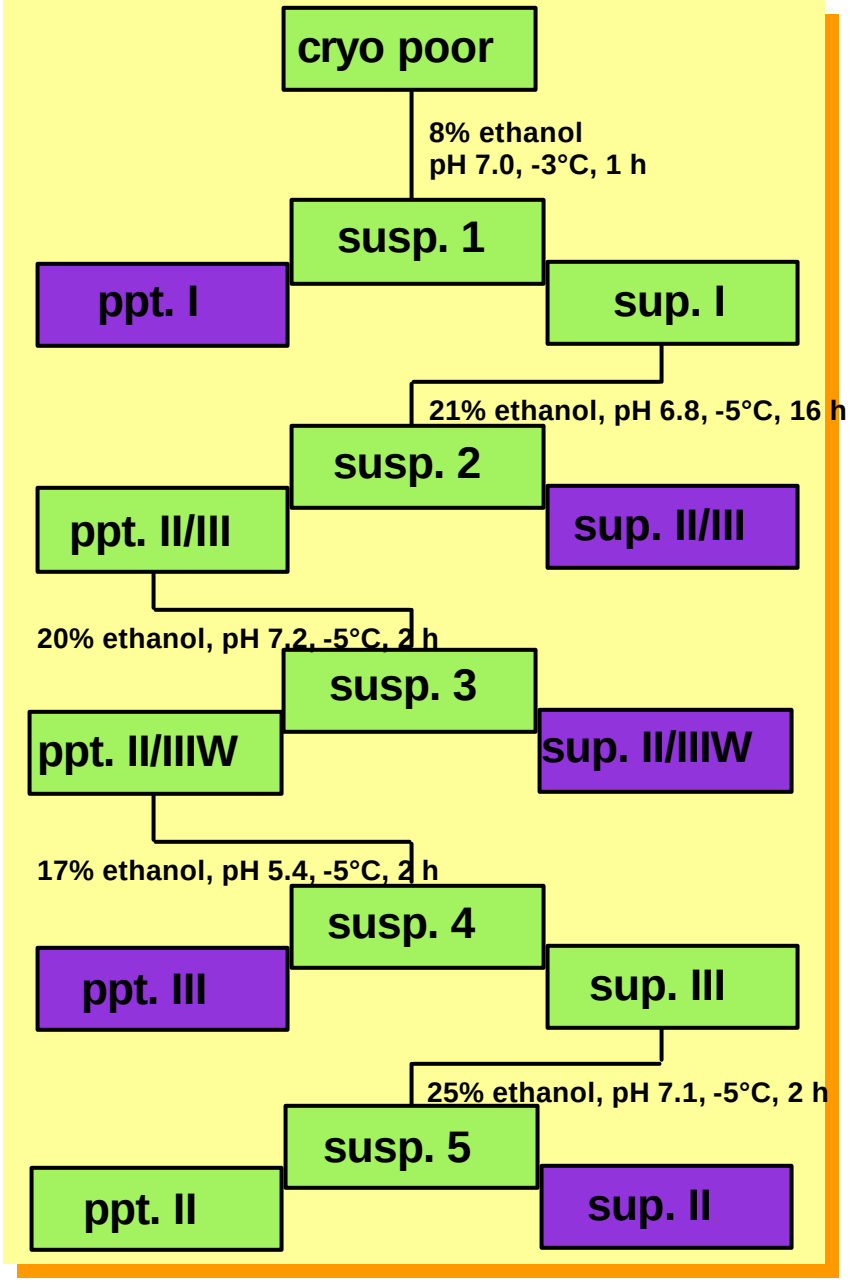
PEI

Virus Transmissions by Blood Products since 1985

Group of Product	Method of Inactivation	Transmitted Virus	Number of Transmissions	Year
PPSB	b-PL, UV	HIV	>10	1989/90
Factor VIII	S/D-treatment	HAV	>80	1991 ff.
iv-IgG	Cohn fractionation	HCV	>250	1993/94
PPSB	Pasteurisation	HBV	>30	1994
Factor VIII	S/D-treatment	HAV	6	1997

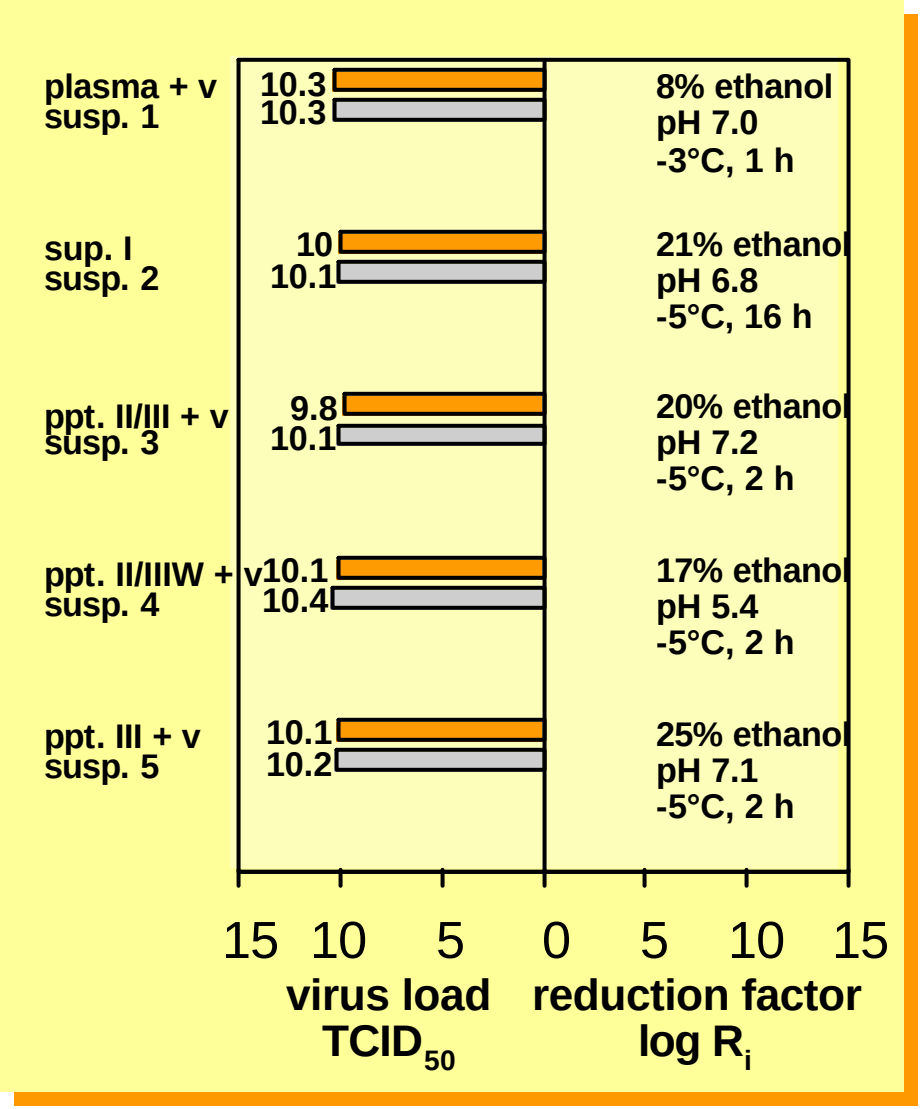
PEI

Cohn-Oncley Fractionation

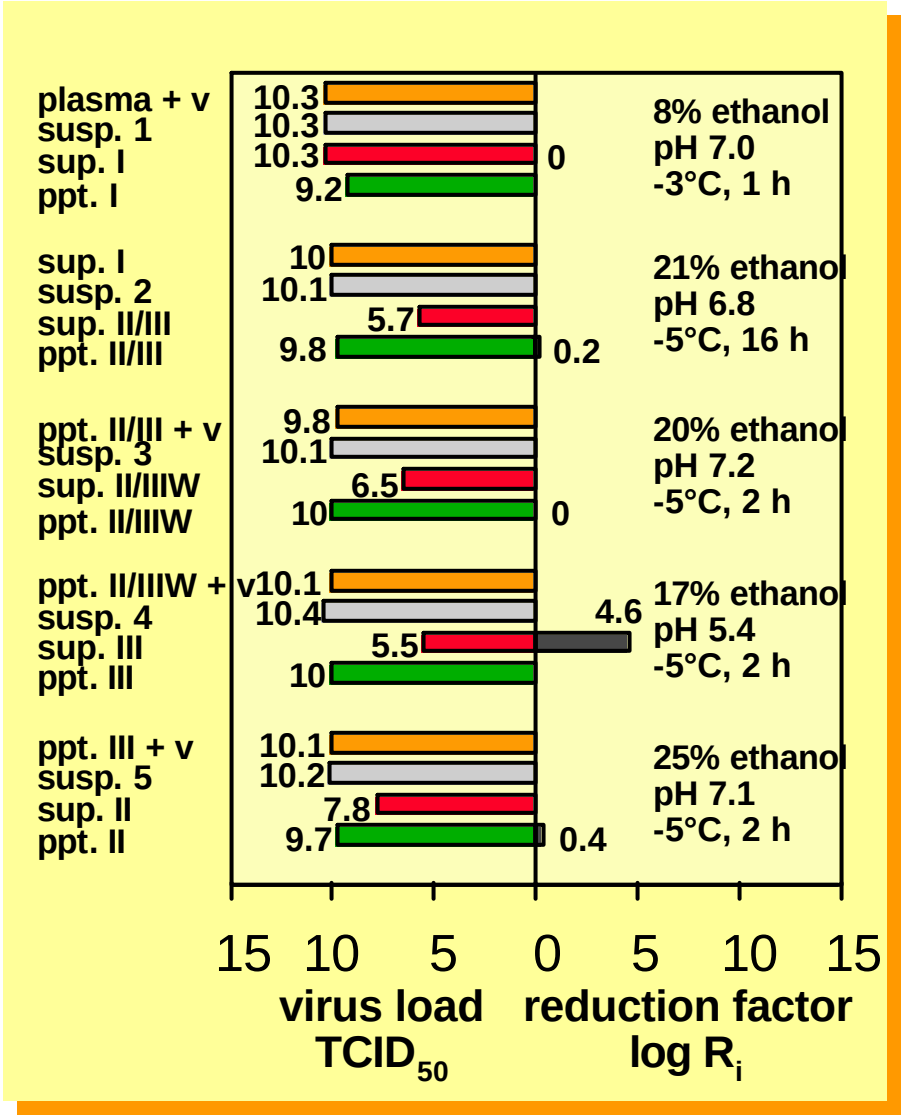


PEI

Cohn-Oncley Fractionation Semliki Forest Virus

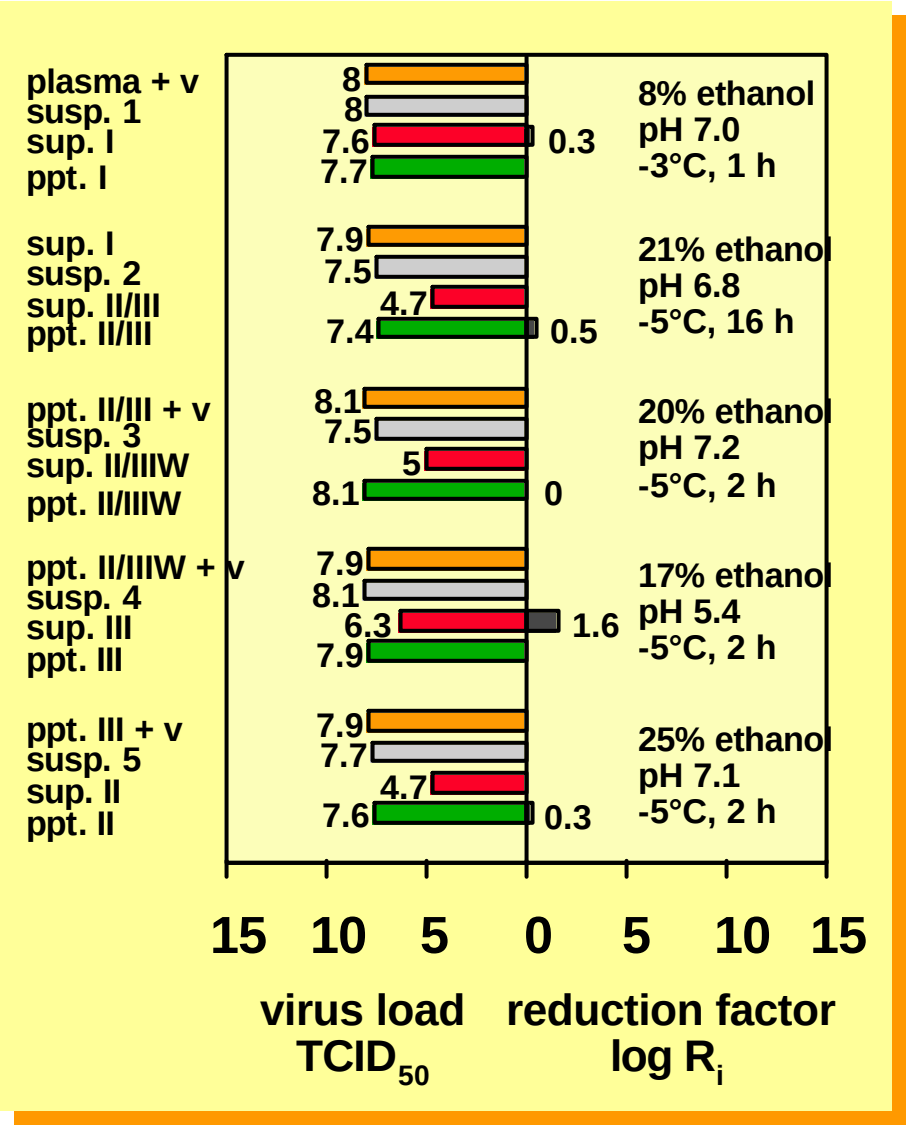


PEI



Cohn-Oncley Fractionation Semliki Forest Virus

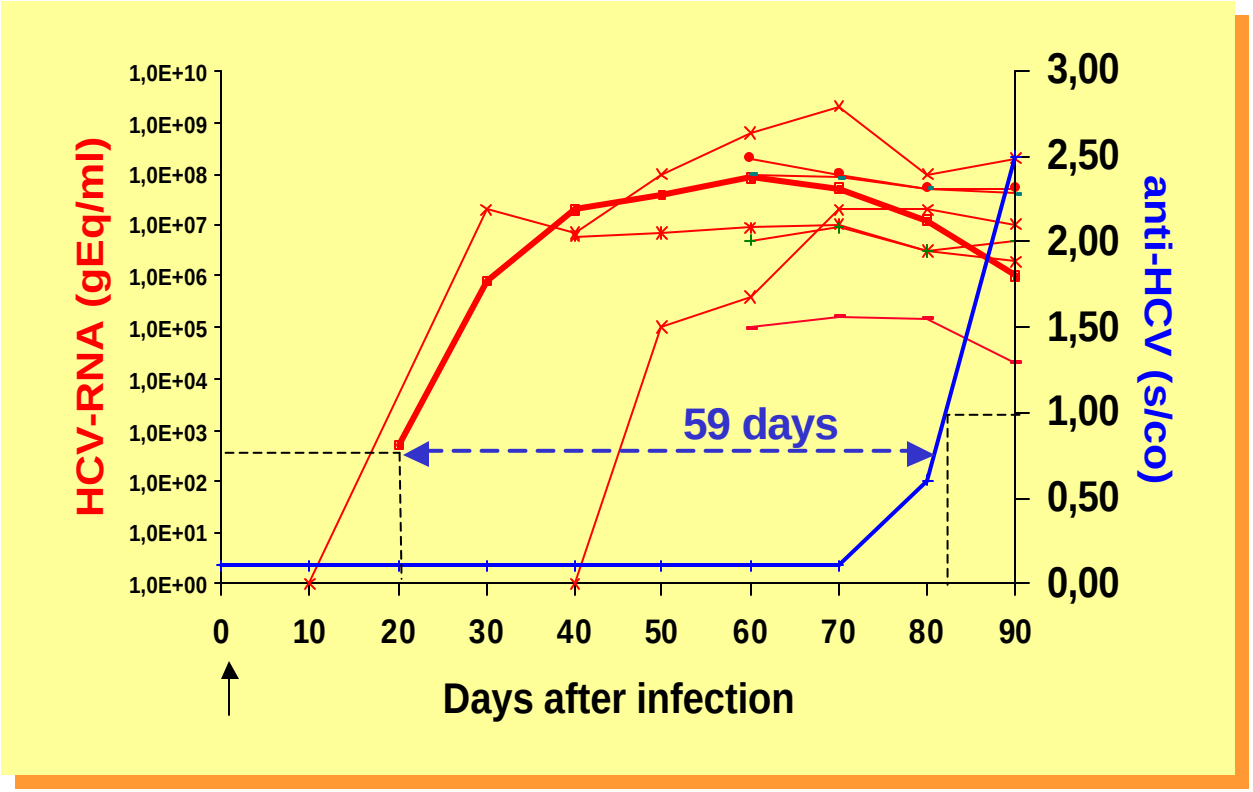
PEI



Cohn-Oncley Fractionation Bovine Viral Diarrhea Virus

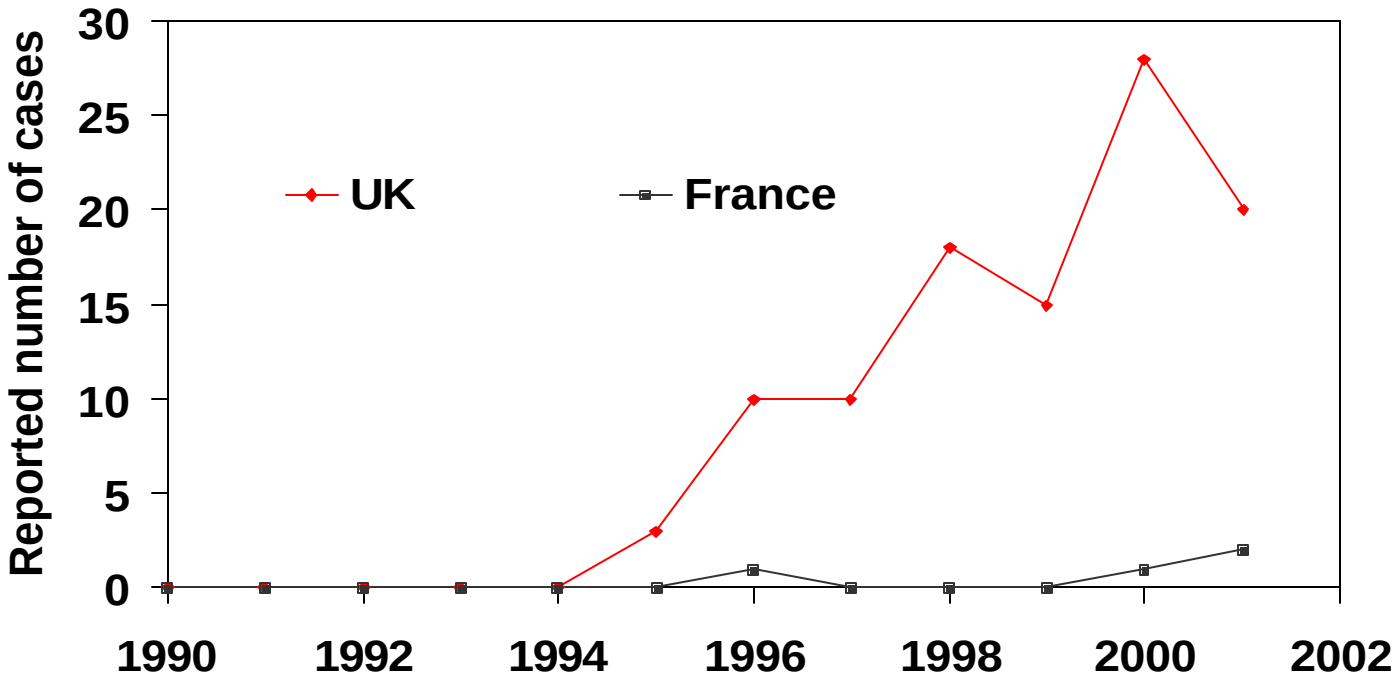
PEI

Viremia during the "diagnostic window" HCV



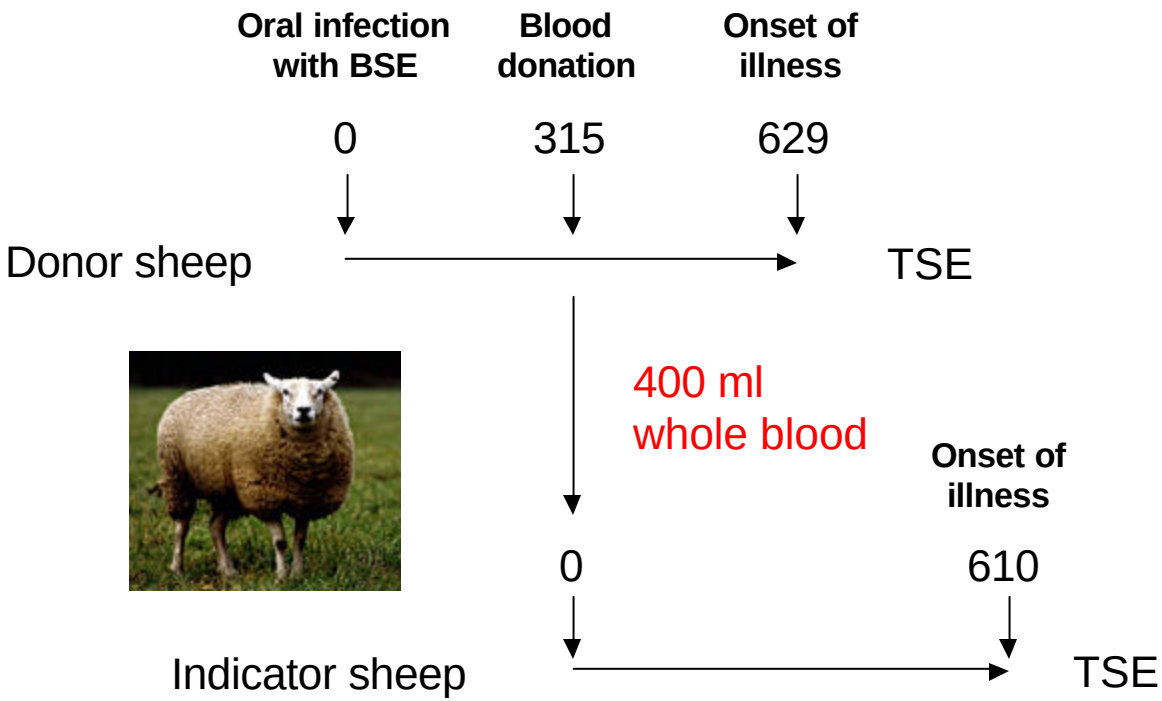
PEI

vCJD cases



PEI

The „Houston“-Experiment



PEI

TSE transmission by blood after oral BSE infection

Stage of disease (days post infecti-on)	Number of donors (ARQ/ARQ)	Number of re-cipients (NZ,ARQ/ARQ)	No. rec. clinical diseases	Incubation time (days)	Survival period (days)
Preclinical (318-669)	5	5	1	610	1208-1251
Preclinical, serially killed (269-293)	4	6	1	536	846-887
Preclinical, serially killed (386-397)	4	7	0	-	1168-1181
Clinical (589-671)	4	5	0	-	76-577
Positive control	-	10	2	605, 627	663-741
Negative control	7	12	0	-	521-893

F. Houston, pers. comm., London, 19 June 2002
http://www.socgenmicrobiol.org.uk/JGVDirect/default.htm

PEI

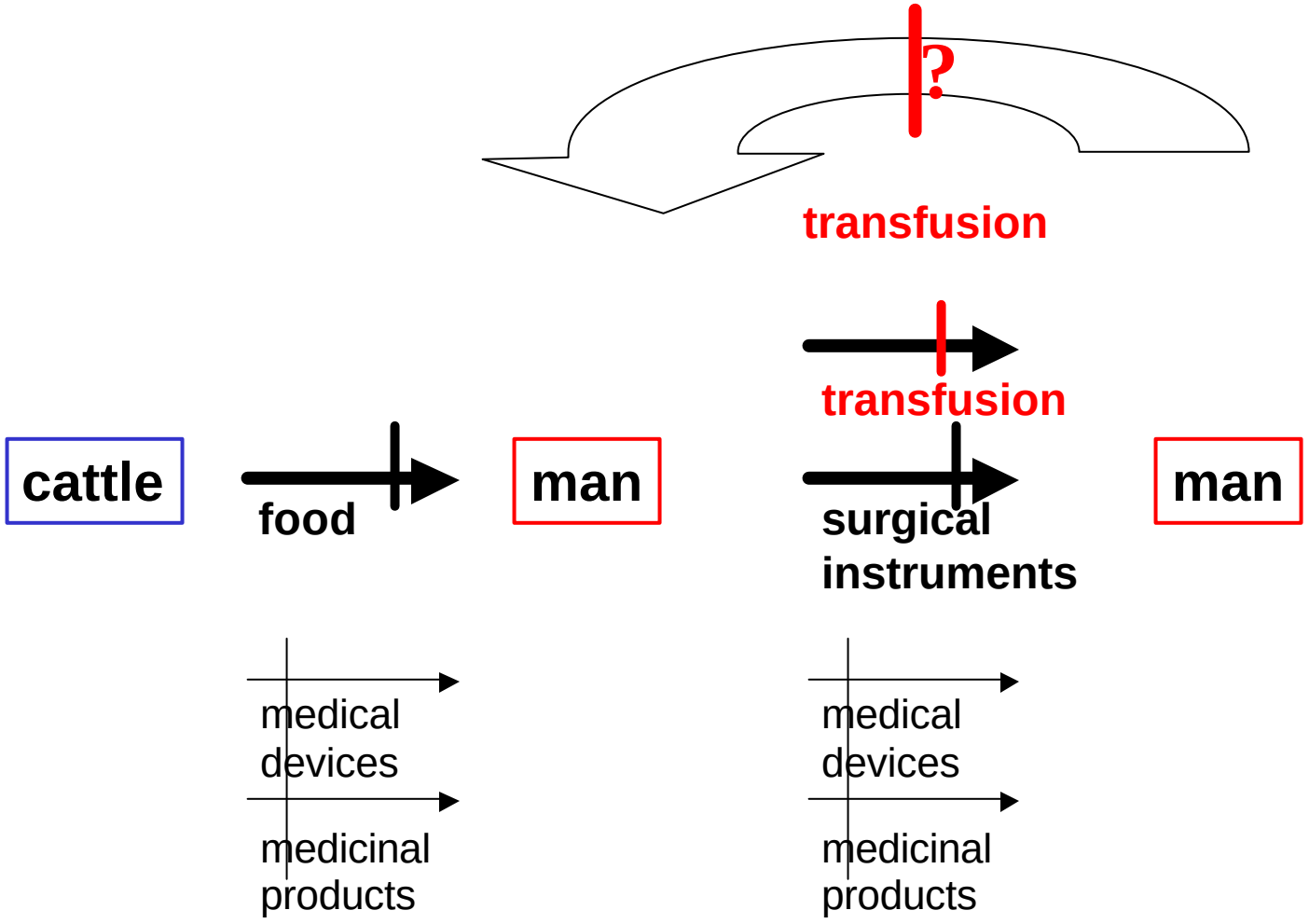
TSE transmission by blood of sheep naturally exposed to scrapie

Stage of incubation (age of donors in days)	Number of donors (VRQ/VRQ)	Number of re-cipients (NZ, VRQ/VRQ)	No. rec. clinical diseases	Incubation period (days)	Survival period (days)
Preclinical (217-247)	3	6	0	-	493-521
Preclinical (455-489)	3	6	0	-	614-648
Preclinical (708-854)	3	6	2	660, 672	648-740
Preclinical/clinical (1082-1138)	2	3	2	575, 737	740
Negative controls	8	16	0	-	46-545

F. Houston, pers. comm., London, 19 June 2002
http://www.socgenmicrobiol.org.uk/JGVDirect/default.htm

PEI

vCJK Transmission



PEI

International Biologics Issues

- Potency
- Safety

PEI

Last four cases of HIV transmission by transfusions in Germany

PEI-no.	Age of recipient	Date of transmission	Date of anti-body detec-tion	PCR result (copies/ml)
6656-1998	>80	01.06.1998	28.10.1998	
7037-2000	>90	21.06.2000	30.08.2000	
6947-2000	<10	03.07.2000	05.09.2000	
679-2001	>70	21.10.2000	23.01.2001	

PEI

Possible causes for not detecting the HIV infections

1: Unusual HIV subtype?
2: Test failure? Handling?
3: Diagnostic window?
4: Attraction of persons at risk through remuneration?

PEI

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6947-2000	<10	03.07.2000	05.09.2000	
679-2001	>70	21.10.2000	23.01.2001	

Infection risk:

Sex with black African (French passport)

Sex in Kenia

Sex with a casual partner during a party

Homosexual

PEI

Last four cases of HIV transmission by transfusions in Germany

PEI-no.	Age of recipient	Date of transmission	Date of anti-body detec-tion	PCR result (copies/ml)
6656-1998	>80	01.06.1998	28.10.1998	>25,000
7037-2000	>90	21.06.2000	30.08.2000	>75,000
6947-2000	<10	03.07.2000	05.09.2000	>40,000
679-2001	>70	21.10.2000	23.01.2001	>250,000

Introduction of HIV-NAT?

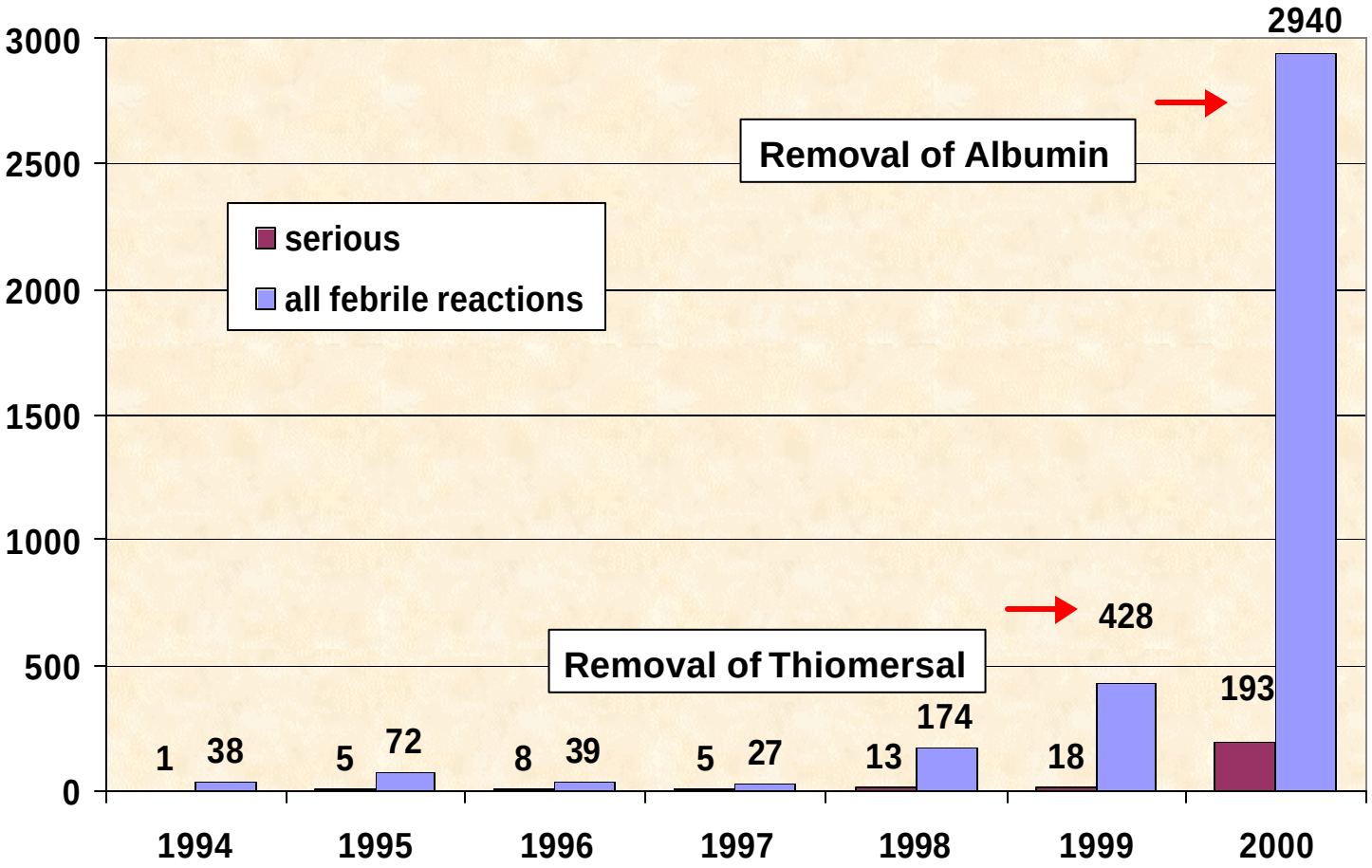
PEI

International Biologics Issues

- Potency
- Safety
- Acceptability of residual risk

PEI

Fever Reactions after Tick-borne Encephalitis Vaccine in Germany between 1994 - 2000



PEI

Marketing Authorization for anti-TNF Proteins

	USA	EU
Etanercept (Embrel)		
Rheumatoid Arthritis	Nov. 1998	Feb. 2000
Infliximab (Remicade)		
Crohn's disease	Aug. 1998	Aug. 1999
+ Rheumatoid Arthritis	Nov. 1999	June 2000

PEI

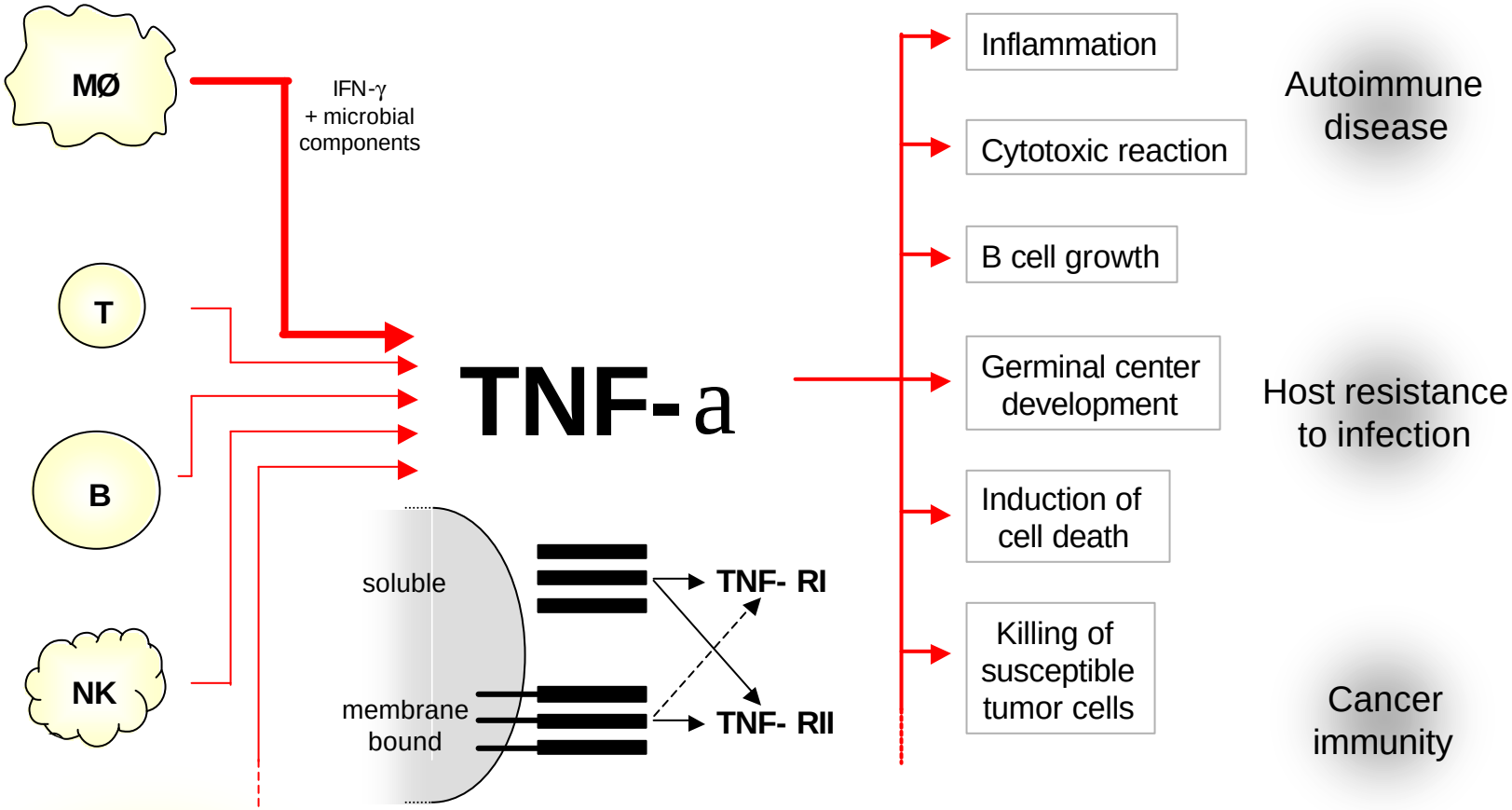
Deaths after administration of Infliximab

Reports to the PEI until 31 Dec. 2001

Adverse event	Crohn's disease	Rheumat. Arthritis	GvHD	Others
Sepsis, severe infections	3	9	4	2
Myocard infarction	1	1		-
Carcinoma	1	-		-
Multi-organ failure	1	-		-
Lung embolism	0	2		-
Aneurysm	1	-		-
Liver failure			3 (2 sepsis)	-
Cerebral bleeding			1(infection)	-
Progression of original disease			2	1
Sum	7	12	7	3

PEI

Pleiotropic TNF-a effects



- Vascular endothelial cells
- Keratinocytes
- Smooth muscle cells
- And many others...

PEI

International Biologics Issues

- Potency
- Safety
- Acceptability of residual risk
- Pharmakovigilance

PEI