Perception of Blood Safety in Europe

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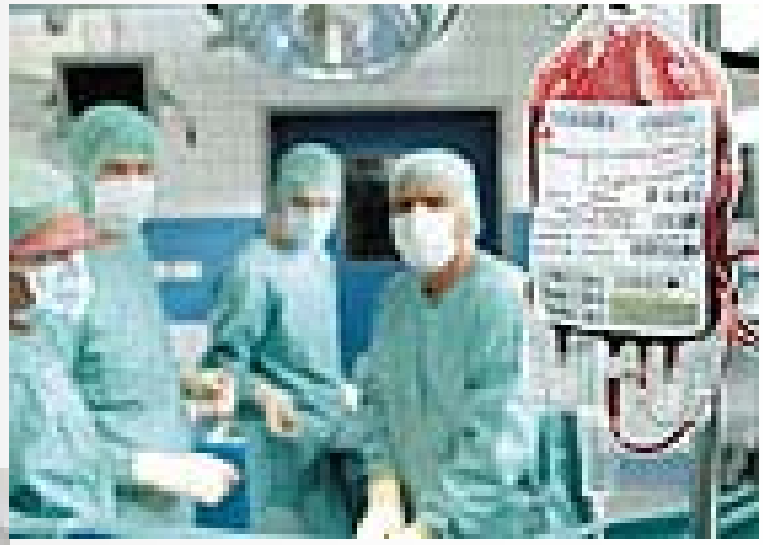
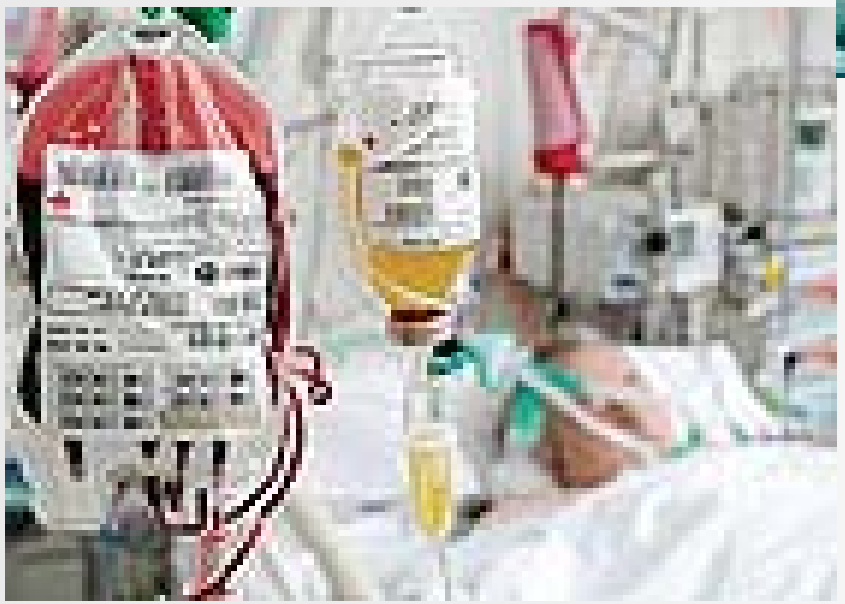
Blood as Source of Life-Saving Medicines

Blood donations are processed into „blood components“, red cells, platelets, plasma for Transfusion „plasma derivatives“, e.g. coagulation factors for haemophilia





For state-of-the-art medicine performance, blood transfusion and plasma products are indispensable!

The HIV shock

- For example, the life of a hemophilia patient had been characterized by pain, crippling, and early death, until in the 1960ies substitute therapies became available
- In the early enthusiasm about a fundamental improvement of life expectancy and quality of life, little attention was paid to virus transmission
- The massive transmission of HIV by blood products in the early 1980ies was one of the worst disasters of modern medicine, and caused dramatic reactions of industry and regulators to increase safety
- In public perception and for health politicians, safety of blood products is still a priority issue

Regulatory Background

- Blood and plasma products have long been considered as replacement of physiological substances, which can only be a benefit, but not harmful to the patient
- As a consequence of the disaster of HIV transmissions in the early 80ies, this view changed. Plasma-derived products became subject to the pharmaceutical legislation in the year 1989 (Directive 89/381/EEC)
- The transfusion products (blood components) remained unregulated on the European level until the year 2002

Europe

- In Europe, there are the national states, like e.g. France, Germany, or the United Kingdom



PEI

- The European Union (EU) and the European Economic Area (EEA), are the European Community (EC)

EMEA

- The Council of Europe: "UN-like", more than 40 member states and observers beyond Europe; European Departement for Quality of Medicines and Health Care (EDQM)

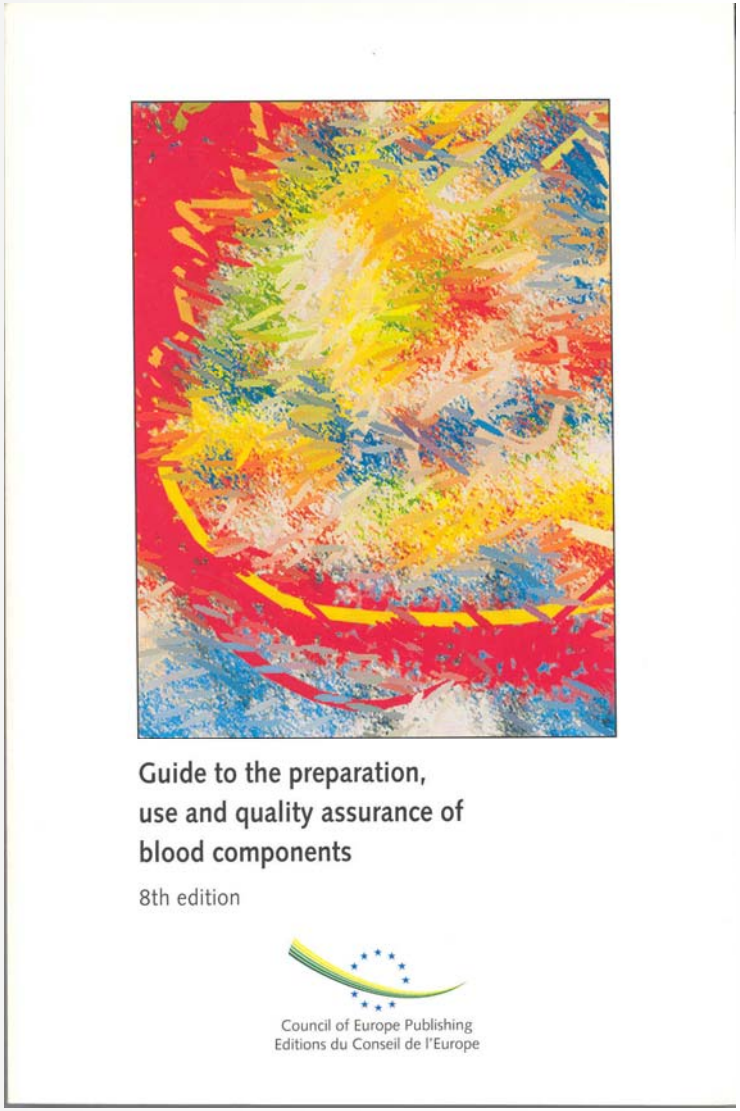
COUNCIL OF EUROPE CONSEIL DE L'EUROPE

PhEur

EC= EU + EEA (Norway, Iceland, Liechtenstein)

History of Blood Systems in Europe

- National blood systems have a long history, with considerable diversity of organisation, regulatory oversight, responsibilities
- The most influential regulatory document used to be to Council of Europe *Guide*; however, it has no mandatory character
- This situation was addressed by the “blood directive” 2002/98/EC



DIRECTIVE 2002/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 27 January 2003

setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC

- "It is essential, that whatever the intended purpose, Community provisions should ensure that blood and its components are of comparable quality and safety throughout the blood transfusion chain in all Member States, bearing in mind the freedom of movement of citizens within Community territory."

→ *Comment: The aim is not free movement of ("open market" for) blood components for transfusion*

Blood Regulators

- European Communities
  - Directive 2002/98/EC of Council and Parliament
  - Directives Commission assisted by a Scientific Committee
    - 2004/33/EC, technical requirements
    - 2005/61/EC, haemovigilance
    - 2005/62/EC, quality system
- German Federal Ministry of Health
  - Transfusion Act (TFG) of 1998
- Bundesärztekammer (Medical Association), in liaison with the PEI
  - Guidelines on the Collection of Blood and Blood Components and on the Use of Blood Products (Haemoptherapy)

Regulatory Oversight in Europe

- European legislation regulating
  - plasma derivatives (regulated as pharmaceuticals)
  - blood components (national level, but European standards)
  - related in vitro diagnostic devices (CE mark)
- Marketing authorisation, EMEA guidance (*)
- European Pharmacopoeia (PhEur) monographs (*)
- Continuous GMP surveillance
- Official Medicines Control Laboratory (OMCL) batch release (*)
- Testing of random samples from the market
- Hemovigilance and pharmacovigilance
- Competence to impose mandatory requirements/precautions

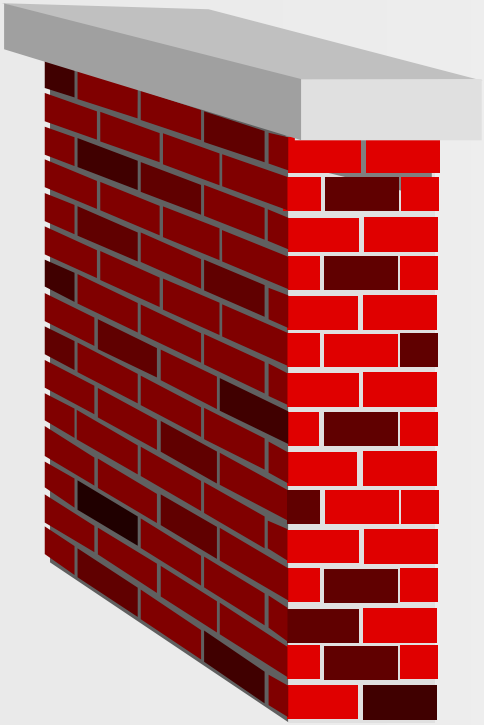
* for all medicinal products manufactured from pooled plasma

Donor criteria

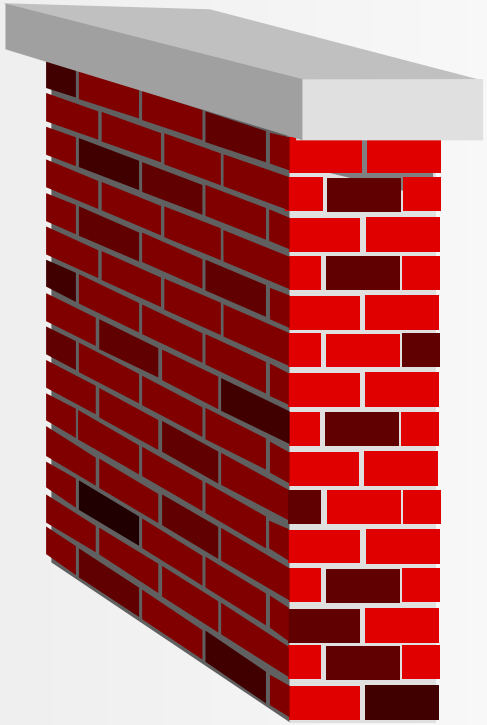
- Directive 2004/33/EC provides legally binding criteria in its ANNEX III: „ELIGIBILITY CRITERIA FOR DONORS OF WHOLE BLOOD AND BLOOD COMPONENTS“
- These state-of-the art requirements build on previous EC Recommendation 98/463/EC on the suitability of blood and plasma donors and the screening of donated blood, the Council of Europe guide, the monographs of the European Pharmacopoeia, particularly in respect of blood or blood components as a starting material, and recommendations of the World Health Organisation (WHO)
- They apply to the collection and testing of human blood and blood components, whatever their intended purpose, including plasma for fractionation

Three walls protecting from transmission of pathogens

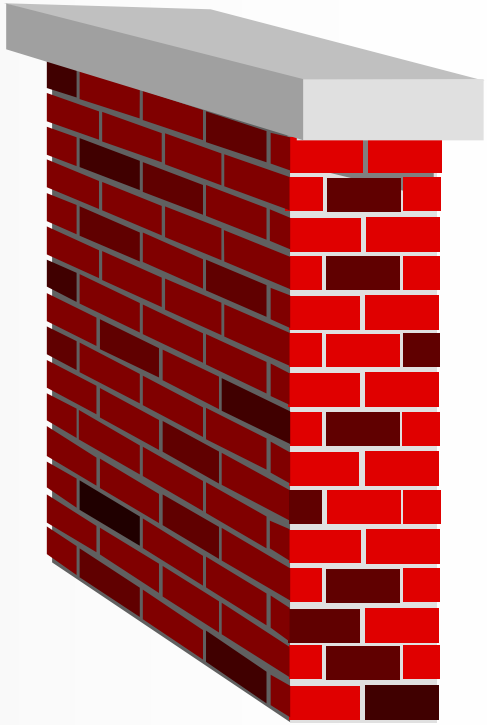
adapted from: N Dhingra, WHO Conference on SARS, Kuala Lumpur, 17-18 June 2003



donor criteria

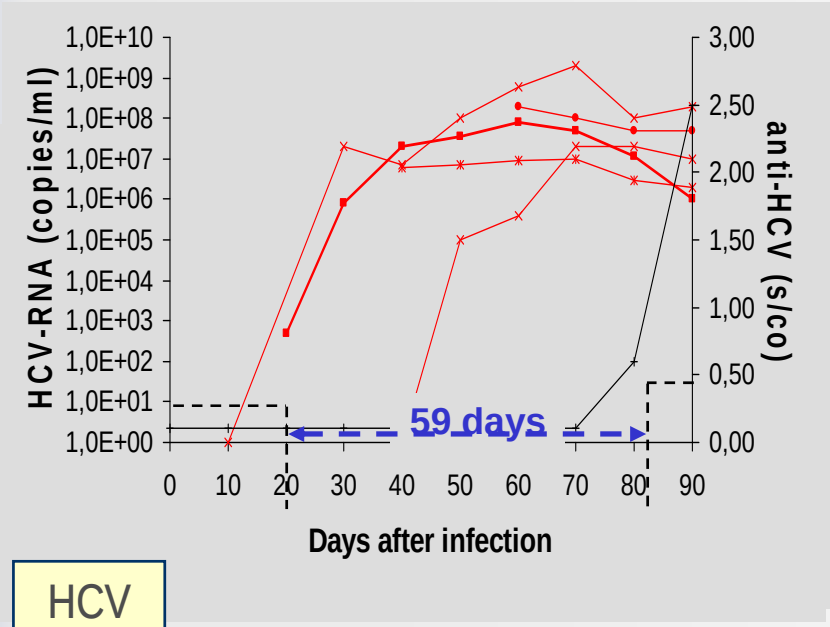


testing



inactivation, removal

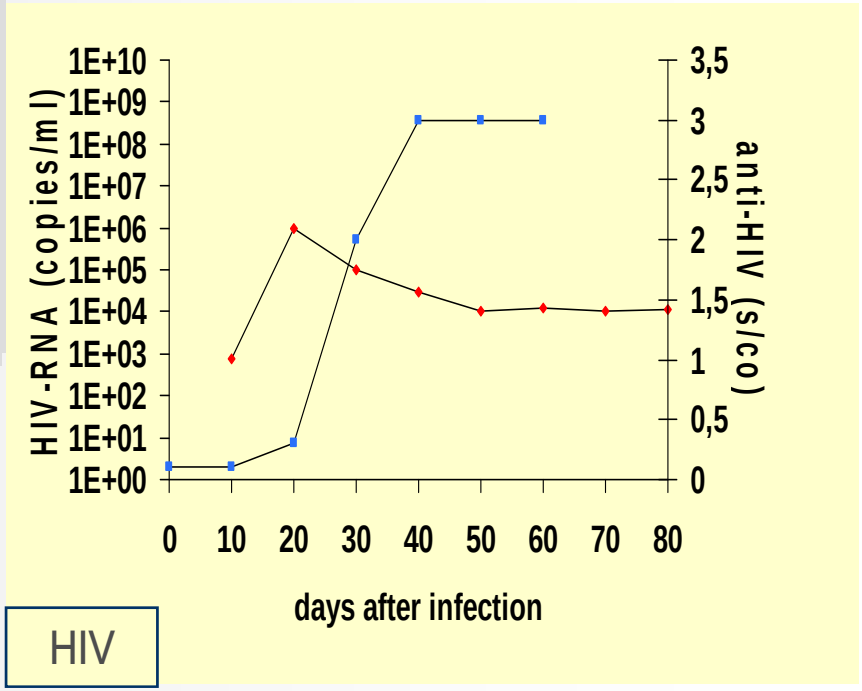
Testing: NAT reduces the diagnostic window period



HCV

M. Nübling et al.

detectable RNA (red cuve/dots) occurs much earlier than antibody response (black curve/blue dots)

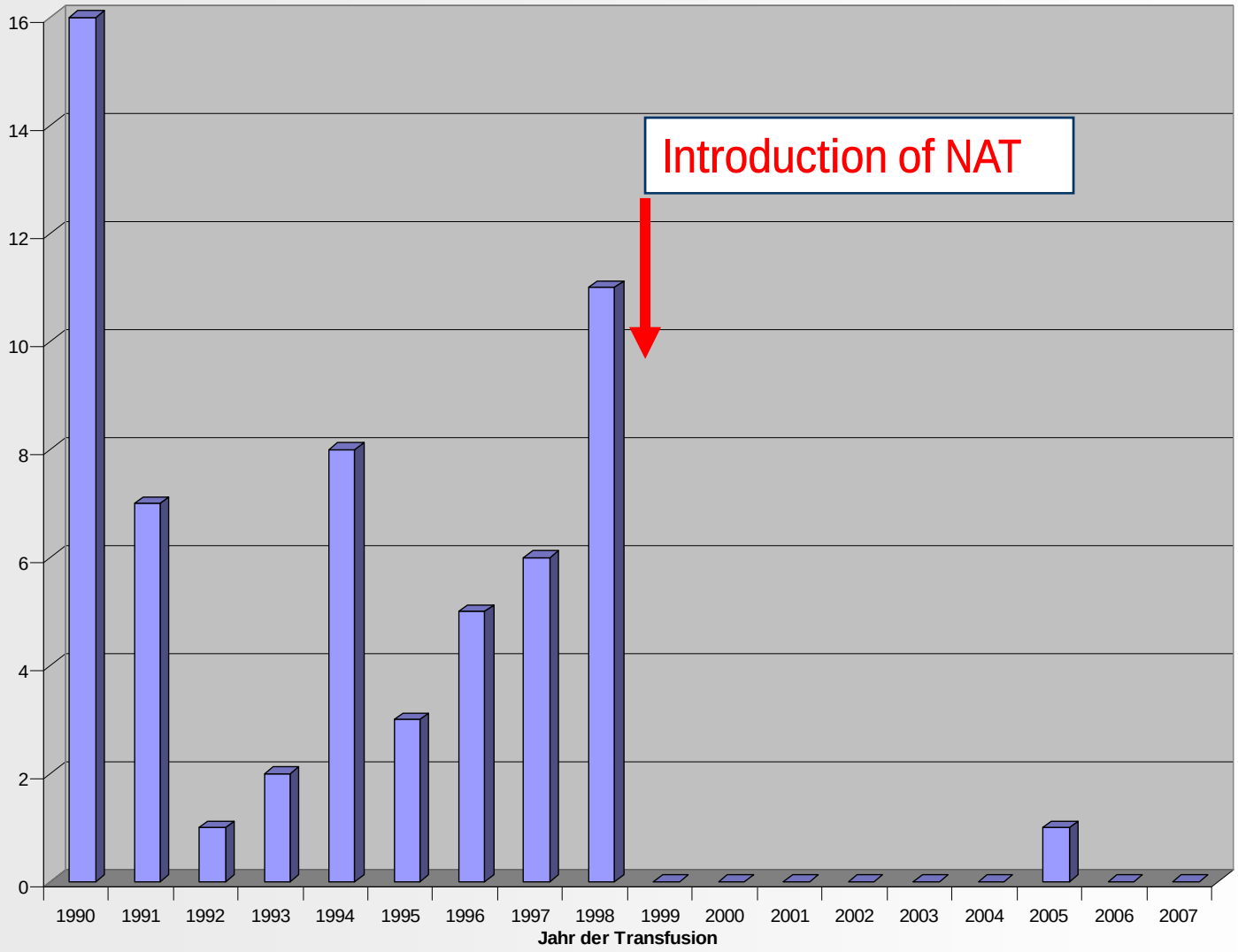


HIV

Effectiveness of NAT Testing in Transfusion Medicine

- The PEI mandated in Germany NAT-testing of blood components for transfusion
  - for HCV (1 April 1999)
  - and for HIV (1 May 2004)
- Transmissions via blood components observed since introduction of NAT in Germany [ca. 4.5 million whole blood donations per year]
  - One single case of HCV transmission in 2006 [E. Kretzschmar et al. Vox Sanguinis (2007) 92, 297–301]
  - One single case of HIV transmission in 2007; first case since 2001

Pharmacovigilance: Transmissions of Hepatitis C Virus via Blood Components, by Year of Transfusion 1990-2007



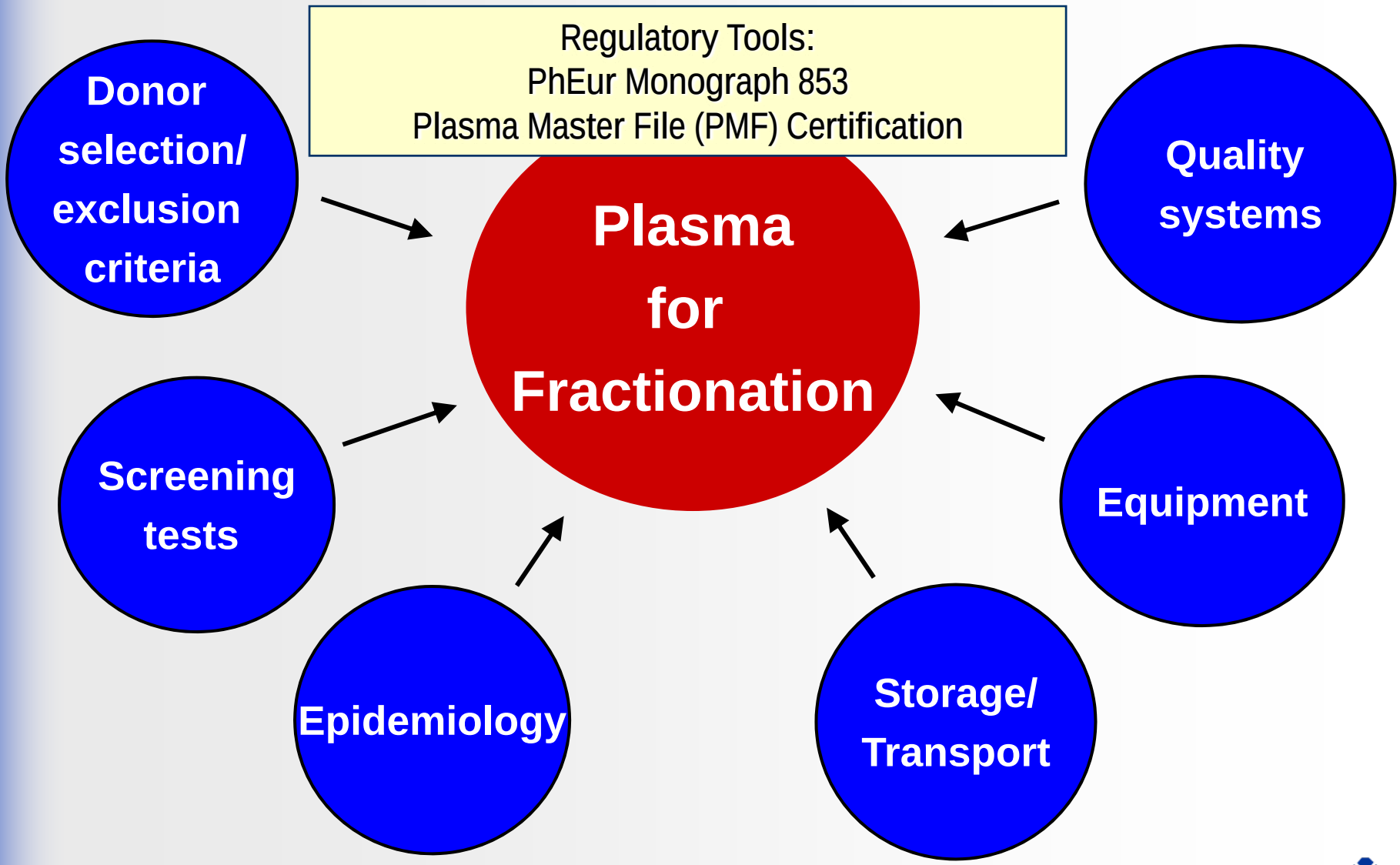
Quality of Plasma Derivatives

- Plasma-derived medicinal products are inherently variable:
  - Biological nature
  - Methods
- Principles to assure quality, safety and efficacy
  - Quality of starting material (e.g plasma for fractionation)
  - Control of manufacturing process
  - Product compliance (Standardisation of methods: raw material testing, in-process testing, finished product testing, stability testing)
  - Adherence to GMP

➲ A biological medicinal product (blood product) is unique with respect to quality design

➲ Quality cannot be tested into a product, but is determined by design

Quality of plasma for fractionation



Plasmapools before HCV NAT:

Initial anti-HCV screening test	Anti-HCV positive pools (anti-HCV 2nd)	No. of plasma pools tested	No. of HCV-PCR positive plasma pools
none	+++	8	8 (100%)
anti-HCV 1st	+/-	85	65 (76%)
anti-HCV 2nd	-	123	49 (39%)

M. Nübling et al.

HCV NAT in plasma pools became obligatory by revision of the PhEur Monograph “Human Plasma for Fractionation” 2001:0853

Effect of viral nucleic acid testing on contamination frequency of manufacturing plasma pools

C. Micha Nübling, Uwe Unkelbach, Michael Chudy, and Rainer Seitz

Transfusion, 2008

Manufacturing plasma pools (1996, 2006)

11 different manufacturers, different geographic origins

analysed by Cobas S201 with TaqScreen

reactives resolved with AmpliScreen assays

TABLE 1. Manufacturing plasma pools analyzed in TaqScreen multiplex assay followed by discriminatory AmpliScreen assays

Year	HCV RNA positive	HIV-1 RNA positive	HBV DNA positive	Unresolved
1996	17.8% (155/873) 95% CI, 15.3%-20.5%	0.8% (7/873) 95% CI, 0.3%-1.6%	0.5% (4/873) 95% CI, 0.1%-1.2%	3% (26/873) 95% CI, 2.0%-4.3%
2006	0.3% (1/331) 95% CI, 0%-1.7%	0% (0/331) 95% CI, 0%-1.1%	0% (0/331) 95% CI, 0%-1.1%	3.6% (12/331) 95% CI, 1.9%-6.2%

Virus elimination: Only few transmissions by industrial plasma products since 1985; none after 1997 (last HAV transmission by a FVIII product)

- Chemical inactivation
- Inactivation by heat
- Removal by virus filters
- Removal by alcohol fractionation

Product	Inactivation by	Virus	No. of Transmissions	Year
PPSB	β-Propiolacton, UV	HIV	>10	1989/90
Factor VIII	Solvent/ Detergent	HAV	>80	1989 ff.
iv-Ig	Cohn Fractionation	HCV	>250	1993/94
PPSB	Pasteurization	HBV	>30	1994

Validation according to EMEA Guideline CPMP/BWP/268/95

Safety of blood products in the EC

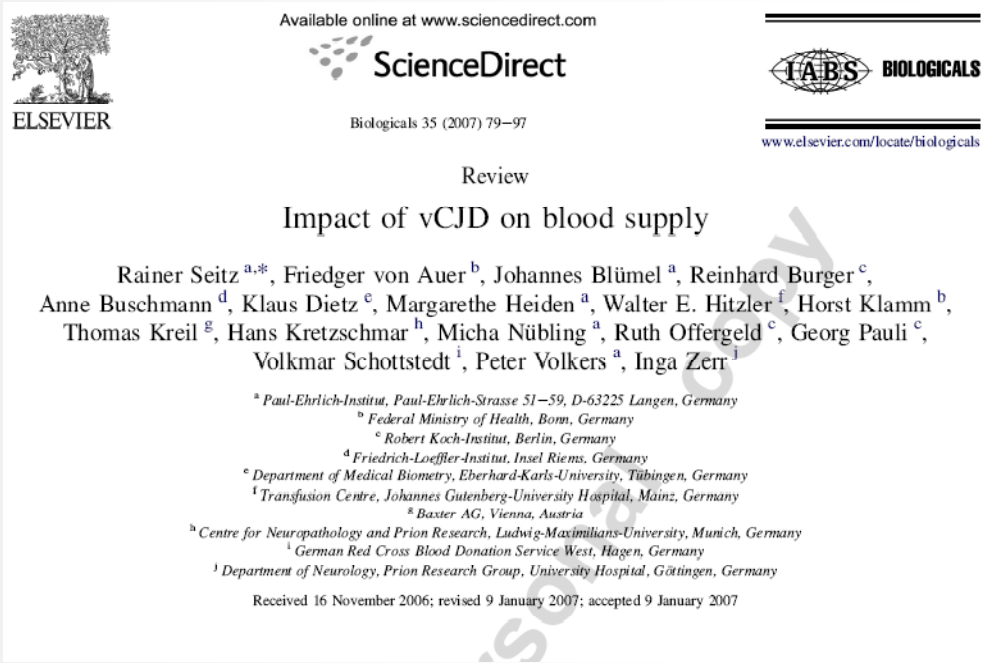
- Commitment of blood services and industry
- Commitment of health politicians, strong legislation, reinforcement and continuous surveillance by authorities
- Advanced technology
  - Virus marker testing
    - For blood components according to national regulations
    - for plasma pools mandatory HCV NAT; NAT against further viruses (HIV, HBV, HTLV, HAV, B19) performed on a voluntary basis by industry
  - State-of-the-art blood banking and donor management
  - State-of-the-art manufacture of plasma derivatives with virus elimination steps, with experimentally validated efficacy

➔ No documented virus transmission by plasma products licensed within the European Community since > 10 years

Addressing infectious risks

- New viruses
  - SARS, WNV, H5N1
- Parasites
  - Malaria, Chagas
- Prion diseases
  - vCJD

- The battle against infections and the struggle for blood safety are closely interrelated !



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Review

Impact of vCJD on blood supply

Rainer Seitz [a,*], Friedger von Auer [b], Johannes Blümel [a], Reinhard Burger [c], Anne Buschmann [d], Klaus Dietz [e], Margarethe Heiden [a], Walter E. Hitzler [f], Horst Klamm [b], Thomas Kreil [g], Hans Kretzschmar [h], Micha Nübling [a], Ruth Offergeld [c], Georg Pauli [c], Volkmar Schottstedt [i], Peter Volkers [a], Inga Zerr [j]

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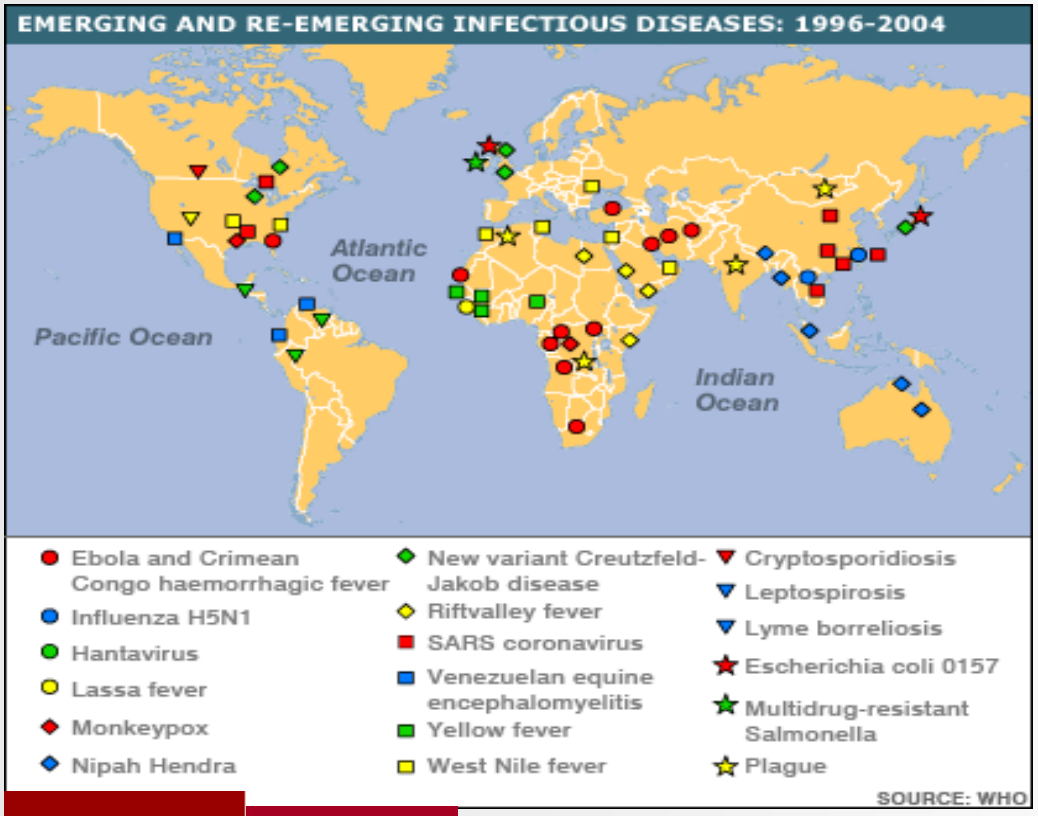
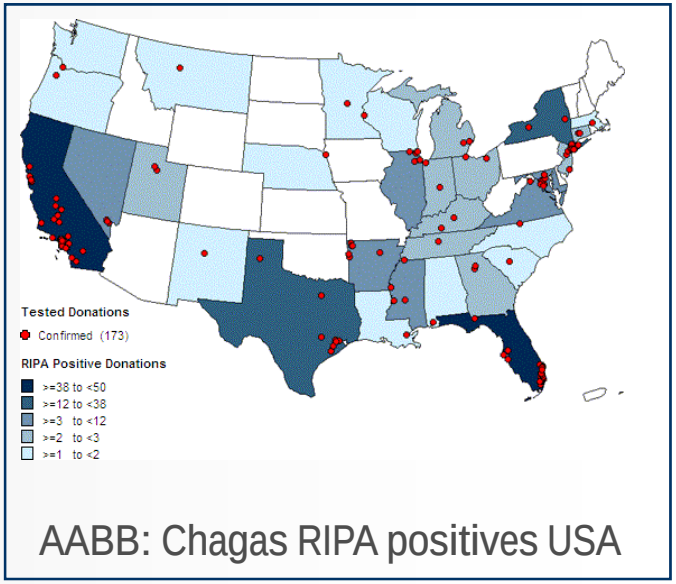
Pathogen Threats



BBC NEWS 24 Aug 07



AABB: Chagas RIPA positives USA

2.1 billion airline passengers are traveling each year.

Infections are a global problem necessitating global collaboration!

WHO Report: http://www.who.int/bloodsafety/en/

Country	Region	Total Population (millions)	HIV Prevalence (% ages 15-49 [range])	Health Expenditure per capita (US$)	Donation per 1000 population
Argentina	AMRO	38,4	0.6 [0.3–1.9]	1.067	19,57
Brazil	AMRO	183,9	0.5 [0.3–1.6]	597	16,56
USA	AMRO	295,4	0.6 [0.4–1.0]	5.711	47,19
Ethiopia	AFRO	75,6	[0.9 – 3.5]	20	0,32
Kenya	AFRO	33,5	6.1 [5.2–7.0]	65	3,58
Lesotho	AFRO	1,8	23.2 [21.9–24.7]	106	1,67
Swaziland	AFRO	1	33.4 [21.2–45.3]	324	8,50
South Africa	AFRO	47,2	18.8 [16.8–20.7]	669	22,51
Netherlands	EURO	16,2	0.2 [0.1- 0.4]	2.987	39,22
Denmark	EURO	5,4	0.2	2.762	69,54
Egypt	EMRO	72,6	<0.1	235	2,31
India	SEARO	1.087,10	0.9 [0.5 – 1.5]	82	4,07
Australia	WPRO	19,9	0.1	2.874	49,16
Japan	WPRO	127,9	<0.1	2.244	29,42

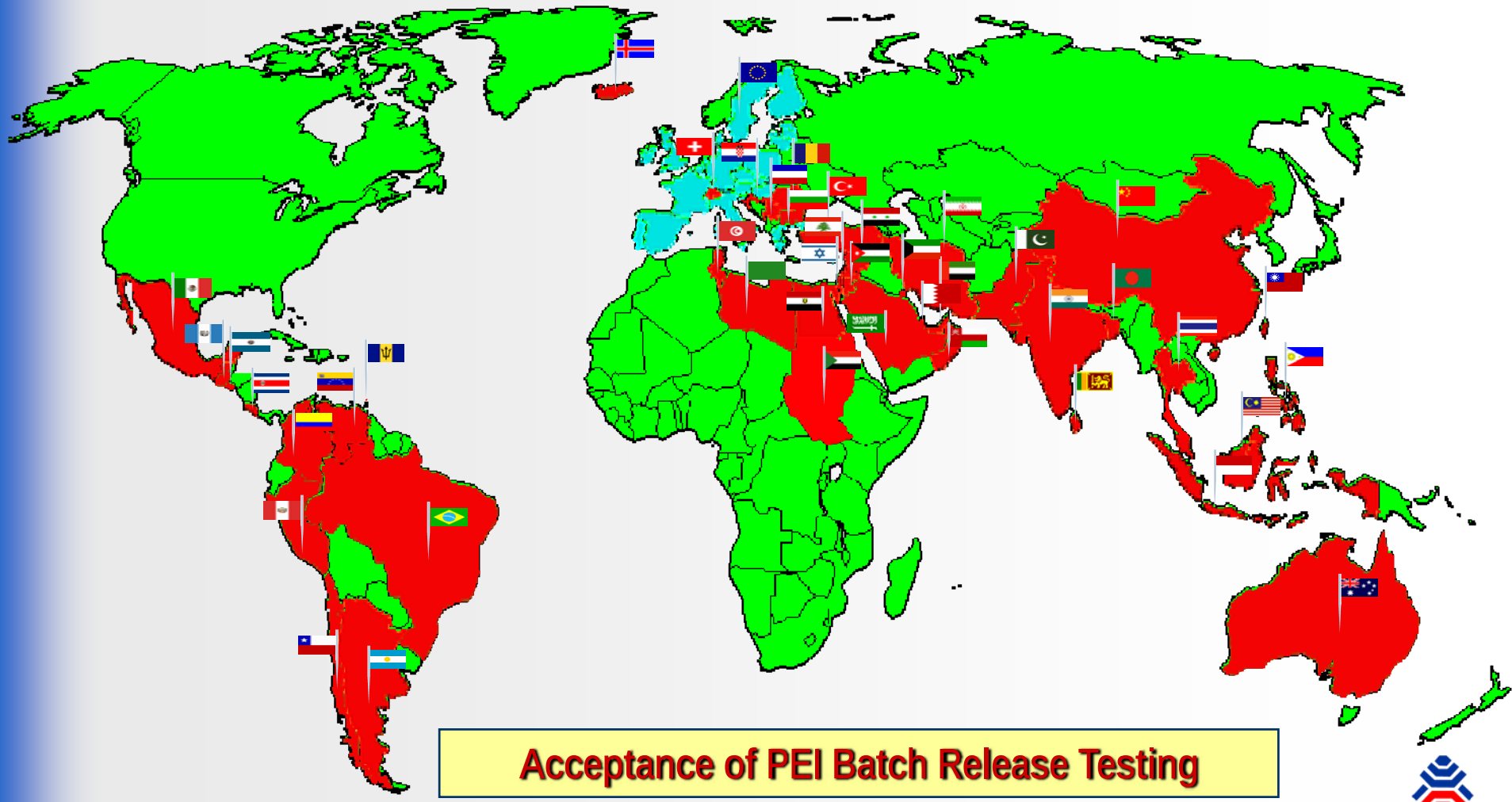
New health technologies: Pathogen inactivation

- Pro
  - Methods available or under development for blood components (e.g. plasma, platelets)
  - Inactivation of many pathogens beyond the range tested for and leukocytes
- Con
  - Limited efficacy against certain viruses (e.g. parvovirus B19) and bacteria (e.g. pseudomonas aeruginosa, spores)
  - Involve chemicals and/or physical treatment; potential toxicity or detrimental impact on liable cells or proteins need to be addressed. Full battery of toxicology testing and clinical studies needed
  - Cost

Emerging problem: counterfeits

- The blood product sector is characterized not only by altruistic blood donation, but is also a multimillion market
- There is an increasing number of counterfeits:
  - Plasma derivatives, e.g. albumin
    - very different quality from reasonable to ineffective to dangerous
    - obscure origin; no information about plasma source, testing, inactivation
  - IVD
    - e.g. ineffective test kits against HIV, HBV, HCV
- Counterfeits tend to be sold in regions where the damage may be particularly high:
  - without stringent regulatory control
  - with unfavorable epidemiology

Worldwide collaboration, e.g. official batch release networks



Optimal Use is another Element of Safety:

Technical Meeting of Blood Experts related to vCJD transmission, Luxembourg, 20 January 2004
SUMMARY STATEMENT

- "There was agreement that optimal use of blood may further reduce the risk of transmission of vCJD by avoiding unnecessary exposure to allogeneic blood transfusion. In addition avoiding unnecessary transfusion may improve the availability of blood for transfusion; this is turn may facilitate the introduction by Member States of additional donor deferrals if required."

- "Participants requested the Commission to build on earlier initiatives at the EU level to promote the optimal use of blood and blood components throughout the EU."

Initiative for optimal Use

- Under the German EU-Presidency, 1999 Expert Meeting in Wildbad Kreuth: „Blood Safety in the European Community: An Initiative for Optimal Use“
- Continuation with further expert meetings (e.g. haemophilia treatment, transfusion) envisaged

Perspective

- The standards of safety of both blood components for transfusion and plasma derived products in the EC are remarkably high
- Nevertheless, there are considerable challenges ahead, such as global spread of new or re-emerging pathogens, new technologies, optimal use of blood products

We have good standards, but should stay alert !