PEI Working for Blood Safety

Prof. Rainer Seitz

Paul-Ehrlich-Institut
Paul-Ehrlich-Straße 51-59
63225 Langen
GERMANY

📞 +49 (0) 6103 77 2600
✉️ +49 (0) 6103 77-1250

Email: haematologie@pei.de
Homepage: http://www.pei.de
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.
In Europe, there are the **national states**, like e.g. France, Germany, or the United Kingdom.

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

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)

**EC = EU + EEA**
(Norway, Iceland, Liechtenstein)
Role of the PEI in Europe

The PEI is the competent higher authority for blood products in Germany

- Both blood components for transfusion and plasma derivatives are considered medicinal products, and are regulated under the German Drug Law

The PEI is one of the leading regulatory agencies in the field of blood products in the European Community

- contributing to the activities of the EMEA: centralised procedure, scientific committees
- contributing to the work of the EDQM: European Pharmacopoeia, scientific transfusion committee
National blood systems have a long history, with considerable diversity of organisation, regulatory oversight, responsibilities.

The most influential regulatory document used to be the Council of Europe Guide; however, it has no mandatory character.

This situation was addressed by the “blood directive” 2002/98/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
- 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 (Haemotherapy)
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

M. Nübling et al.

Detectable RNA (red curve/dots) occurs much earlier than antibody response (black curve/blue dots)
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
- 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

Introduction of NAT
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

Donor selection/exclusion criteria

Screening tests

Epidemiology

Storage/Transport

Equipment

Quality systems

Regulatory Tools:
PhEur Monograph 853
Plasma Master File (PMF) Certification
Plasmapools before HCV NAT:

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

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>
<thead>
<tr>
<th>Year</th>
<th>HCV RNA positive</th>
<th>HIV-1 RNA positive</th>
<th>HBV DNA positive</th>
<th>Unresolved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1996</td>
<td>17.8% (155/873)</td>
<td>0.8% (7/873)</td>
<td>0.5% (4/873)</td>
<td>3% (26/873)</td>
</tr>
<tr>
<td></td>
<td>95% CI, 15.3%-20.5%</td>
<td>95% CI, 0.3%-1.6%</td>
<td>95% CI, 0.1%-1.2%</td>
<td>95% CI, 2.0%-4.3%</td>
</tr>
<tr>
<td>2006</td>
<td>0.3% (1/331)</td>
<td>0% (0/331)</td>
<td>0% (0/331)</td>
<td>3.6% (12/331)</td>
</tr>
<tr>
<td></td>
<td>95% CI, 0%-1.7%</td>
<td>95% CI, 0%-1.1%</td>
<td>95% CI, 0%-1.1%</td>
<td>95% CI, 1.9%-6.2%</td>
</tr>
</tbody>
</table>
Virus elimination: Only few transmissions by industrial plasma products since 1985; none after 1997 (last HAV transmission by a FVIII product)

<table>
<thead>
<tr>
<th>Product</th>
<th>Inactivation by</th>
<th>Virus</th>
<th>No. of Transmissions</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPSB</td>
<td>β-Propiolacton, UV</td>
<td>HIV</td>
<td>&gt;10</td>
<td>1989/90</td>
</tr>
<tr>
<td>iv-Ig</td>
<td>Cohn Fractionation</td>
<td>HCV</td>
<td>&gt;250</td>
<td>1993/94</td>
</tr>
<tr>
<td>PPSB</td>
<td>Pasteurization</td>
<td>HBV</td>
<td>&gt;30</td>
<td>1994</td>
</tr>
</tbody>
</table>

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

Validation according to EMEA Guideline CPMP/BWP/268/95
PEI in European Centralised Procedure 1995 - 2005

CHMP (co-) rapporteurship for PEI-relevant products [hum.]
## OMCL Batch Release (Plasma Products excl. Immunoglobulins)

<table>
<thead>
<tr>
<th>Category</th>
<th>2004</th>
<th>2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Release</td>
<td>597</td>
<td>511</td>
</tr>
<tr>
<td>EU-Certificates</td>
<td>801</td>
<td>986</td>
</tr>
<tr>
<td>EU-Certificates in combination with National</td>
<td>278</td>
<td>274</td>
</tr>
<tr>
<td>Release of Package Batches</td>
<td>354</td>
<td>535</td>
</tr>
<tr>
<td>Recognition of EU-Certificates of other OMCL</td>
<td>157</td>
<td>93</td>
</tr>
<tr>
<td>Duplicates</td>
<td>166</td>
<td>129</td>
</tr>
<tr>
<td>Test Reports</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Certificates of Plasma Pool Origin</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td><strong>Total Batch-Certificates</strong></td>
<td>2406</td>
<td>2612</td>
</tr>
<tr>
<td>Plasma Pool-Certificates</td>
<td>1644</td>
<td>1537</td>
</tr>
<tr>
<td><strong>Total issued Certificates</strong></td>
<td>4050</td>
<td>4159</td>
</tr>
</tbody>
</table>

![Pie Chart showing distribution of batches by region](chart.png)

- **GE**: 47%
- **UK**: 19%
- **IT**: 12%
- **NL**: 3%
- **BE**: 3%
- **AU**: 16%
PEI and IVDs

until 2003
- Assessment and approval of IVDs for the German market
- Batch Release of IVDs

Worldwide reputation of PEI

since 2004
- Assessment of IVDs for the Common Market in Europe
- Focus on „high-risk“ IVDs
  - HIV, HBV, HCV
  - Blood groups
- Batch release testing of IVDs

Safety testing of biologicals (e.g. blood safety testing)
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!
Pathogen Threats

2.1 billion airline passengers are traveling each year.

Infections are a global problem necessitating global collaboration!
<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Total Population (millions)</th>
<th>HIV Prevalence (% ages 15-49 [range])</th>
<th>Health Expenditure per capita (US$)</th>
<th>Donation per 1000 population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argentina</td>
<td>AMRO</td>
<td>38.4</td>
<td>0.6 [0.3–1.9]</td>
<td>1.067</td>
<td>19.57</td>
</tr>
<tr>
<td>Brazil</td>
<td>AMRO</td>
<td>183.9</td>
<td>0.5 [0.3–1.6]</td>
<td>597</td>
<td>16.56</td>
</tr>
<tr>
<td>USA</td>
<td>AMRO</td>
<td>295.4</td>
<td>0.6 [0.4–1.0]</td>
<td>5.711</td>
<td>47.19</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>AFRO</td>
<td>75.6</td>
<td>[0.9 – 3.5]</td>
<td>20</td>
<td>0.32</td>
</tr>
<tr>
<td>Kenya</td>
<td>AFRO</td>
<td>33.5</td>
<td>6.1 [5.2–7.0]</td>
<td>65</td>
<td>3.58</td>
</tr>
<tr>
<td>Lesotho</td>
<td>AFRO</td>
<td>1.8</td>
<td>23.2 [21.9–24.7]</td>
<td>106</td>
<td>1.67</td>
</tr>
<tr>
<td>Swaziland</td>
<td>AFRO</td>
<td>1</td>
<td>33.4 [21.2–45.3]</td>
<td>324</td>
<td>8.50</td>
</tr>
<tr>
<td>South Africa</td>
<td>AFRO</td>
<td>47.2</td>
<td>18.8 [16.8–20.7]</td>
<td>669</td>
<td>22.51</td>
</tr>
<tr>
<td>Netherlands</td>
<td>EURO</td>
<td>16.2</td>
<td>0.2 [0.1- 0.4]</td>
<td>2.987</td>
<td>39.22</td>
</tr>
<tr>
<td>Denmark</td>
<td>EURO</td>
<td>5.4</td>
<td>0.2</td>
<td>2.762</td>
<td>69.54</td>
</tr>
<tr>
<td>Egypt</td>
<td>EMRO</td>
<td>72.6</td>
<td>&lt;0.1</td>
<td>235</td>
<td>2.31</td>
</tr>
<tr>
<td>India</td>
<td>SEARO</td>
<td>1.087.10</td>
<td>0.9 [0.5 – 1.5]</td>
<td>82</td>
<td>4.07</td>
</tr>
<tr>
<td>Australia</td>
<td>WPRO</td>
<td>19.9</td>
<td>0.1</td>
<td>2.874</td>
<td>49.16</td>
</tr>
<tr>
<td>Japan</td>
<td>WPRO</td>
<td>127.9</td>
<td>&lt;0.1</td>
<td>2.244</td>
<td>29.42</td>
</tr>
</tbody>
</table>
WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices

Paul-Ehrlich-Institut
WHO Collaborating Centre for Quality Assurance of Blood Products and in vitro Diagnostic Devices
WHO Initiatives

Blood transfusion safety
- Global Collaboration for Blood Safety (GCBS)
- World Blood Donor Day
- Guidance documents

Blood products and related biological substances; Expert Committee on Biological Standardization (ECBS)
- Guidelines, e.g. on plasma for fractionation
- International standard preparations
- Blood Regulators Network (BRN)

International Conference of Drug Regulatory Authorities (ICDRA)
- Recommendation to set up a blood regulators network
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

Acceptance of PEI Batch Release Testing
“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
The PEI is one of the leading authorities committed to the regulation of blood products and international cooperation. 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.