Safety Assessment and Regulatory Issues in Blood Products

Improving World Health Through Regulation of Biological Medicines
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Plasma Products

- Industrially purified preparations (e.g. coagulation factors, antibodies) are manufactured from pooled plasma from a great number of donors.

- In the past, patients suffering from haemophilia had to face pain, impairments and death at an early age; modern medicinal products help improve their quality of life and increase their life expectancy.
Blood as a Medicinal Product

Blood donations are processed to become "blood components": Red blood cells, platelets (for haemostasis), plasma.

Blood transfusions are indispensable in modern medicine!
Regulatory Control of Medicinal Products in Europe: National and EC Activities

- Marketing authorization
- Official batch release
  - Plasma derivatives, not recombinant products
- Regular surveillance inspections
  - Ensuring e.g. Good Manufacturing Practice (GMP)
- Postmarketing surveillance
  - CAP (Centrally Authorised Products) testing: spot checks with random sampling from the market
- Pharmacovigilance
  - Reports of adverse events, regulatory measures
  - Periodic Safety Update Reports (PSUR)
Challenges / past events

overview
Safety Problems

- Pathogen transmission
  - Virus infections:
    - Human immune deficiency (HIV)
    - Liver infection: Hepatitis B (HBV), Hepatitis C (HCV)
  - Prions?
    - Creutzfeldt-Jakob-Disease
- Immunological incompatibility or allergic reactions
- Blood clotting (thromboses)
On the basis of 81 million donations per year in 178 countries worldwide only around 60% would be subject to stringent safety requirements. Deficient regulatory systems or lack of appropriate tests still account for about 40% of donations globally, i.e.

32 million donations are not or not completely tested

http://www.who.int/bloodproducts/ivd/en/
### WHO Global Database 2001 - 2002

<table>
<thead>
<tr>
<th>Virus / Bacterium</th>
<th>Donations Not Tested</th>
<th>Deficient Testing (about 35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>357.036</td>
<td></td>
</tr>
<tr>
<td>HBV</td>
<td>401.933</td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>1.948.933</td>
<td>28.802.809</td>
</tr>
<tr>
<td>Treponema pallidum (Syphilis)</td>
<td>2.595.344</td>
<td></td>
</tr>
</tbody>
</table>

### Risk of Pathogen Transmission by Blood Products per Year

<table>
<thead>
<tr>
<th>Virus / Disease</th>
<th>Prevalence in Donor Blood</th>
<th>Minimum Risk of Infection (no test at all)</th>
<th>Maximum Risk of Infection (no test plus deficient testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1/1.000 – 1/10.000</td>
<td>35 – 357</td>
<td>2.915 – 30.000</td>
</tr>
<tr>
<td>HBV</td>
<td>1/10.000</td>
<td>40</td>
<td>3.000</td>
</tr>
<tr>
<td>Syphilis</td>
<td>no data</td>
<td>no data</td>
<td>no data</td>
</tr>
</tbody>
</table>

- Epidemiology varies in different countries/continents
- Other viruses may have to be considered in other countries/continents
- B19 infections are only serious for certain risk groups (e.g. sickle cell anaemia in Africa, pregnant women)
- Virulence may depend on epidemiological factors (e.g. HAV)
- HTLV (I + II) and HCMV are mainly cell associated.
# Regulation of Blood Screening in Germany

<table>
<thead>
<tr>
<th>Viral marker</th>
<th>Licence Date of First Assay</th>
<th>Introduction of Testing</th>
<th>Test Mandatory Since</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>1 Mar 1976</td>
<td>End of seventies</td>
<td>1980</td>
</tr>
<tr>
<td>Anti-HIV</td>
<td>5 Jun 1985</td>
<td>immediately</td>
<td>1 Oct 1985</td>
</tr>
<tr>
<td>Anti-HCV</td>
<td>5 Jan 1990</td>
<td>1992</td>
<td>1 Jan 1993</td>
</tr>
</tbody>
</table>
### Virus Transmissions by Blood Products in Germany since 1985

<table>
<thead>
<tr>
<th>Group of Product</th>
<th>Method of Inactivation</th>
<th>Transmitted Virus</th>
<th>Number of Transmissions</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPSB</td>
<td>β-PL, UV</td>
<td>HIV</td>
<td>&gt;10</td>
<td>1989/90</td>
</tr>
<tr>
<td>iv-IgG</td>
<td>Cohn fractionation</td>
<td>HCV</td>
<td>&gt;250</td>
<td>1993/94</td>
</tr>
<tr>
<td>PPSB</td>
<td>Pasteurisation</td>
<td>HBV</td>
<td>&gt;30</td>
<td>1994</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>S/D-treatment</td>
<td>HAV</td>
<td>6</td>
<td>1997</td>
</tr>
</tbody>
</table>
Transmission of vCJD by Blood Transfusion

- Three cases of **probable transmission of vCJD by blood transfusions** have been observed in the UK. They were detected since blood donations, which vCJD patients had given before illness, are followed up
  - Patient diagnosed with vCJD 6.5 years after red blood cells from a donor with vCJD 3.5 years after donation
  - Patient having received red blood cells from donor with vCJD 18 months after donation, died 5 years later from unrelated cause; autopsy vCJD pathogen (prions) in his lymphatic tissue
  - Patient diagnosed with vCJD 8 years after red blood cells from a donor with vCJD 20 months after donation
vCJD Risk of Blood Products?

- Red cell transfusions are large-volume, non-processed single donor blood components
  - If a donor is incubating vCJD, his/her blood may contain prions
  - There is no dilution, nor sufficiently effective removal of prions

- Plasma products are manufactured from large pools of donations, the haemophilia products are highly processed (fractionation, purification)
  - If a donor is incubating vCJD, his/her plasma would be diluted in a large pool
  - For several steps of manufacture, effective removal of prions has been demonstrated experimentally
Precautions

- Refrain from using UK plasma for fractionation
- Exclusion of donors possibly at risk
  - CJD or vCJD of donor or in family
  - Treatment with human pituitary hormone, TX of dura mater or cornea
  - After cumulative stay for \( \geq X \) (*) months in UK between 1980 and 1996
  - After operation/transfusion in the UK
  - Recipients of blood transfusions (*)
- Recall of products, if vCJD donor identified

(*) The measures taken may vary by member state
Available data indicate that the **manufacturing processes for plasma-derived medicinal products would reduce infectivity if it were present in human plasma**. Manufacturers are now required to estimate the potential of their specific manufacturing processes …

A CHPM Note for **guidance on the investigation of manufacturing steps** came into force in October 2004

Bakterial Transfusion Reactions
1995 - 2005

Total Suspected Cases 92
  Causal relationship likely 45
    Contamination of the sample 42
    Unrecognised infection of the donor (Yersinia 3
    enterocolica, E. coli, Malaria)

Total - fatal outcome 15
  Sepsis by pathogens detected in the bag containing 7
  residual sample
  (Yersinia (2x), Staph. aureus, Klebsiella pneumoni-
  ae, Proteus vulgaris, Enterobacter cloacae,
  Strept.pyogenes)
Approaches to Control Potential Viral Contamination of Biologicals
Approaches to Control Potential Viral Contamination of Biologicals

Three principal complementary approaches can be adopted to control potential viral contamination of biologicals:

- selecting and testing source material for the absence of viruses,
- testing the capacity of the production processes to remove or inactivate viruses,
- and testing the product at appropriate stages of production for freedom from contaminating viruses.
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**
Diagnostic Window in HIV Detection

- NAT <500 copies/ml
- HIV single p24 antigen
- HIV Ag/Ab combination
- HIV 1/2 antibody
- HIV 1/2 rapid
- HIV 1/2 antibody
- Current CE-marked by PEI/NB since 2003
- After re-evaluation PEI 1998
- After re-evaluation PEI 1994
- CE-marked not by PEI in 2005
Diagnostic Window in HCV Detection

Current CE-marked Anti-HCV assays by PEI/NB since 2003

- Day delay in detection of HCV

- NAT

- HCV core Antigen

- CE-marked in 2005 not by PEI

- after re-evaluation PEI 1998

- up to 2003
Summary I
Quality Control of Screening Tests

- Crucial parameters: sensitivity and specificity
- Sensitivity: crucial for safety
- Sensitivity: close to 100% with clearly positive samples
- Biological sensitivity: seroconversion panels
- Analytical sensitivity: dilution series
- For antibody tests, analytical sensitivity does not correlate with biological sensitivity
- Analytical sensitivity should not be used for comparison of assays, but for control of consistency of batches
Summary II
Quality Control of Screening Tests

- Specificity: largely economical, logistical and psychological issue, less for safety
- Specificity: >95% with large number of negative samples
- Specificity: >95% with tricky samples
HCV NAT reduces the “window” period by ca. 60 days

The PEI mandated in Germany the NAT-testing for HCV (1 April 1999) and HIV (1 May 2004) of all donations for transfusion
# HCV NAT in Plasma Pools

## Pools 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>

After introduction of HCV NAT, the HCV burden in all plasma pools used in the EC is below the detection limit, ensuring a high safety margin for the virus inactivation steps.

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M. Nübling et al.
Nucleic Acid Amplification Tests: Events in Europe

21 February 1994  Withdrawal of license for Gammagard
24 November 1994  NAT in plasma pools for certain IVIG
27 April 1995  NAT in plasma pools for certain IMIG
14 September 1995  NAT in plasma pools for certain IMIG
7 May 1996  Commitment for HCV NAT in plasma pools (EAPPI)
12 February 1997  Commitment for HCV NAT in plasma pools (EPFA)
21 October 1997  CPMP recommendation for HCV NAT in plasma pools from 1 January 1999
NAT: Appropriate Stage for Testing for Freedom from Contaminating Viruses

1. Single donation
2. Testing pools
3. Minipools
4. Production pools
5. Intermediate products
6. Final products
Appropriate Stage for Testing for Freedom from Contaminating Viruses

It is due to statistics (Poisson distribution) that testing of final products for the presence of viruses (antigen tests, NAT) cannot ensure freedom from contaminating agents.
**Viral Safety of Blood Transfusions after Introduction of NAT**

- The selection of healthy donors and highly developed testing methods have reduced the risk drastically.
- The “residual risk“ of contracting a virus infection through a blood transfusion is extremely low and can only be assessed very roughly:
  - For HIV and HCV it is markedly below 1 : 3,000,000
  - For HBV, NAT is difficult to perform and is not obligatory; in spite of this, only isolated transmissions HBV occur; testing for anti-HBc is currently introduced.
- Experience will show whether new developments in the **pathogen inactivation** of blood components will bring about further progress.
Spontaneous Reports of probable Transmissions of Hepatitis C Virus via Transfusions 1990-2005 (n = 60)

Introduction of NAT
Summary: Importance of in vitro Diagnostics

- First line detection of infectious agents (highest probability in blood donations)
- Crucial for the prevention of transmission of blood-borne pathogens
- Avoiding new starting points for transmission chains
- Impact appropriate control on safety of blood and blood products

Independent control = unbiased control
Principles in the regulatory (independent) evaluation of IVD tests

- “Licensing”
  - Verification of documents
  - Laboratory control
- Official batch (lot) release
  - Verification of documents
  - Laboratory control
- Emergency cases methods
Approaches to Control Potential Viral Contamination of Biologicals

Three principal complementary approaches can be adopted to control potential viral contamination of biologicals:

- selecting and testing source material for the absence of viruses,  
  Testing of blood donations with serological and NA tests
- testing the capacity of the production processes to remove or inactivate viruses,  
  Virus validation studies
- and testing the product at appropriate stages of production for freedom from contaminating viruses.  
  Plasma pool testing with NA tests