First Report of the EID Roundtable

March 10-11, 2004

Brussels, Belgium
The Plasma Protein Therapeutics Association (PPTA) is sponsoring the EID Roundtable. PPTA is a trade association and standards-setting organization that represents the world’s major producers of plasma-derived therapies. PPTA conceived the idea for the Roundtable as a vehicle for enhancing global communication in the area of emerging threats to plasma-derived therapies.

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Emerging Infectious Diseases Roundtable Executive Summary

Background

Regulatory policies addressing emerging infectious diseases (EID) have been developed regionally, based on local laws and regulations. Regulators have no mandate to communicate or work with other regulators throughout the world although, in practice, efforts are being made to improve this situation. However, EIDs have a global effect and regional policies have an impact on companies marketing worldwide. The EID Roundtable was initiated because of the general agreement that a harmonized global approach is needed to react in a timely and efficient way to new emerging pathogens. The EID Roundtable included policymakers from regulatory and standards-setting organizations, representatives of patient groups, international experts in print media, bioethics and risk management, and industry scientists. The goal of the EID Roundtable is to bring together regulators and interested parties to begin dialogue to improve global communications related to decision making in the face of EID threats.

EID Roundtable Format

The first part of the EID Roundtable included presentations from various perspectives of responses to EID threats in four recent experiences. The topics of presentation were variant Creutzfeld-Jakob Disease (vCJD), Parvovirus B19, West Nile Virus (WNV), and Severe Acute Respiratory Syndrome (SARS). The perspectives were from the points of view of regulators, industry scientists, and transfusion medicine/patients. Areas explored in presentations were science, social, political and economic concerns that influenced decisions.

From the presentations, key areas in the management of EIDs were identified. These areas included: 1) scientific risk assessment modeling; 2) manufacturing process, testing and viral inactivation; 3) communication with donors and recipients; 4) donor management; and 5) appropriate clinical product usage. Participants were divided into two discussion groups to address the key areas.

Discussion

The first discussion group focused on the elements of the key areas. Highlights of the discussions on these elements included the following:

Scientific risk assessment: In the face of an emerging threat, the scientific risk assessment is of paramount importance but may be difficult to ascertain. Early in the threat, there is often limited knowledge about the agent causing the disease. It is important to collect data on the suspected agent quickly and this data collection requires a proactive approach. Being able to define the trigger for action is important and requires coordination. The scientific risk assessment should be science-based and free from other influences (e.g., vested interests). For this reason, it was thought that the risk assessment should be performed by independent experts who are provided access to existing data.
The risk assessment should be separated from the policy decision process in order to avoid pre-
decision and premature public assurances.

Manufacturing process, testing and viral inactivation: Regulators need specific information on
products in order to gain a basis for appropriate decisions. This information can only be provided
by industry. At present, there are inherent difficulties in accessing and sharing such data. A more
open approach to communicating EID risk information is needed by all to better facilitate timely
decisions.

Communication with donors and recipients: Regulators and industry have an obligate
responsibility to communicate risks. Early in a threat, such communication is difficult because of
the limited knowledge base. However, there needs to be open dialogue among all parties.

Donor management: Donor exclusions based on epidemiological or other risk factors may be
necessary. It is important to balance safety versus availability of blood products. Differentiation
of risk to products (e.g., transfusable components versus fractionated products) is vital in
determining a donor’s suitability for donation. In any event, it is important to give the appropriate
and responsible message to donors.

Appropriate clinical product usage: It is important to assess the appropriate clinical use of any
blood product against the threat of an EID. “Benchmarking” would be a useful tool in determining
the use of any product versus the risk of an impending EID threat.

The second discussion group focused on the process for continuing dialogue in the area of EID.
The plasma therapies industry is a global industry and the management of EIDs needs to be
driven on a global basis as opposed to locally. Discussants agreed that the forum needs a
framework for continuing the process. Several options were discussed for continuing dialogue to
establish a pathway for handling EIDs on a global basis. Among the discussion points were
rolling the discussions into the existing framework of the World Health Organization’s Global
Collaboration for Blood Safety or the International Association for Biological Safety. Concern was
expressed that overly bureaucratic processes must not be allowed to slow down further program.

Next Steps

Consensus among participants appeared to exist around the need for a framework to address EID
policy-setting with the highest priority being a process to facilitate communication and appropriate
coordination among patients, regulators and industry.

The EID Roundtable will continue with the goals of improving communications globally to address
the threats of EIDs and finding a forum for developing a pathway to develop a “best practices”
guideline. A further roundtable meeting was agreed to be important and worthwhile.
Emerging Infectious Disease Roundtable Report

March 11 2004
The Hilton, Brussels

The Emerging Infectious Disease (EID) Round Table was initiated because of the general agreement that a harmonized global approach is needed to react timely and efficiently to new emerging pathogens. The event was unique in its nature with all stakeholders present who have a view on the issue.

The meeting was divided into two sections. In part one case studies were discussed followed by an examination of each study to map out the critical path for decision making to develop strategies to address EIDs. The case study topics were selected prior to the roundtable by the roundtable planning committee. Participants, representing different perspectives on the individual cases, were asked to present the case studies from their perspective to the roundtable. Following the case study presentations and discussion of those specific cases, the roundtable spent the afternoon analyzing key elements identified from the case study presentations in a broader context of international decision making.

Case studies

Case Study: vCJD in the UK:
The emergence of variant Creutzfeldt-Jakob Disease (vCJD) represents an example of the need for policy setting in the absence of complete information. Significant gaps in knowledge regarding the route of transmission, the nature of the infectious agent, and the epidemiological profile of the disease, persist today. Despite these knowledge gaps international regulatory bodies have developed policies for managing the perceived risk to blood and blood derivatives. These policies vary widely by geographic region and reflect the different perspectives on risk and different tolerances for managing incomplete information about the emergence of infectious diseases.

Presentation from S. Ruiz
Dr. Ruiz's presentation focused on steps taken by European Regulators following the recent report of a possible transmission of vCJD by a blood transfusion in the UK. Existing policies were immediately reevaluated based on all available data. Factors included in the reevaluation were: 1) risk factors, such as residence in the UK; 2) implemented safety measures, such as donor exclusion criteria; and, 3) communication tools, such as the CPMP position statement1. Decisions affecting the plasma industry included: 1) no change to the CPMP position on the recall of plasma derived medicinal

products in case of a donor suspected or diagnosed with classical CJD since it is accepted that the available data indicate that the manufacturing process for plasma derived medicinal products would reduce infectivity if it were present in human blood; 2), a new requirement that manufacturers use available information to analyze the potential of their manufacturing processes to reduce infectivity because it is still unknown to what extent infectivity may be present in human blood in the preclinical phase of the disease. Manufacturers should undertake product specific investigational studies on key steps in the manufacturing process. The CPMP is developing a Discussion document\textsuperscript{2} to provide regulatory guidance on how to investigate manufacturing processes with regard to vCJD; and 3) no harmonized donor exclusion policy among the European Member States, which may cause difficulties in the free movement of starting material, intermediates and final product. To mitigate some of these difficulties, the position statement EMEA/CPMP/BWP/2879/02 states, "countries may still apply a stricter limit than 1 year for exclusion within the country (e.g. 6 months) but will accept plasma-derived medicinal products provided that at least the one year limit is applied”.

Presentation from R. Perry
The second case study was performed from a UK perspective. Dr. Perry outlined findings of the Phillips report, an independent government inquiry on bovine spongiform encephalopathy (BSE) in the UK that was published in 2000. The objective of this inquiry was to establish and review the history of the emergence and identification of BSE and vCJD in the United Kingdom, and the actions taken in response to it up to 20 March 1996. The report concluded that the government acknowledged too late that BSE has been transmitted to humans. The timing of the report coincided with an incoming new government, which felt highly vulnerable and thus adopted a precautionary approach. The government took the lead in assessing human risk and the impact of the precautionary measures, while the scientific progress followed. The political necessity of the initiatives removed the consideration of benefit for costs. If a similar challenge would occur today, certain changes in approach would be recommended. These include: initiation of animal research early; investment in evaluating patterns of blood use and traceability and a comprehensive blood management programme to reduce the population at risk of needing transfusions; and public education about the nature and unavoidability of very small risks in the context of all medical risks, rather than premature and ultimately false assurances of safety. However, the climate in which such an incidence occurs will in the end determine the actions taken.

Roundtable Discussion of Case
vCJD is an example for the interplay of scientific development, political decision making and economic impact. It can be concluded that the UK government implemented sensible measures.

\textsuperscript{2} Discussion paper on the investigation of manufacturing processes for plasma-derived medicinal products with regard to vCJD risk (CPMP/BWP/CPMP/5136/03) London 20 November 2003
Many questions remain about the level of BSE exposure. Is it a UK or a European or a global issue?

Social and political thinking may at times support science or override it.

Absence of evidence of risk is not evidence of absence of risk.

In 1997 the establishment of scientific committees within the institutions of the European Union changed the environment. The science was in place and sufficient information was available, but nevertheless a generous transition time was allowed.

The Australian experience showed that it is wrong to try to reassure the public on false grounds because the general public cannot perceive the implications for therapies. The public has to be permanently and credibly reassured.

Donor exclusion was identified as an important issue for the round table discussion. Blood and plasma have to be differentiated, which was acknowledged by the FDA when no exclusion of plasma donors was required. The situation is different when recovered plasma is used for fractionation. In Australia a review of travel habits was performed as a model for the potential loss of donors. The loss of committed donors after 3 to 4 years was estimated to be around 20%.

The European Union also distinguished between blood and plasma, which is reflected by the responsibilities of the individual EU institutions. The EU commission is responsible for all issues around blood, while the EMEA focuses on plasma related topics.

Manufacturers need to demonstrate clearance of infectious agents. It needs to be discussed whether the related regulations should first be put in place and subsequently supported by data or whether the data should be generated to support the regulatory decision making process. It is in any case important to have an open dialogue between manufacturers and regulatory agencies and to share information.

**Case Study: Parvovirus B19:**
Parvovirus B19 is a non-enveloped virus known to cause infectious disease without serious conditions except in persons with other serious underlying diseases. In the context of plasma protein therapies Parvovirus B19 represents an example for a new paradigm, where the aim is to reduce rather than eliminate the virus load in the manufacturing pool and rely on the inactivation/removal capacity of the manufacturing process.

**Presentation from J. Löwer**
The case study performed from a regulators perspective focused on the facts known about Parvovirus B19 today and strategies for controlling transmission.

Facts about Parvovirus B19:
• virus relatively well known with a significant amount of scientific data and clinical experience available.
• known to be transmitted by plasma derived medicinal products
• study of German haemophilia patients found almost 100% were positive for anti Parvovirus B19 antibodies.  
• prevalence of Parvo B19 in the population makes exclusion of virus impractical
• transmissions associated with highly contaminated plasma pools and DNA containing final products
  - low virus titers might be effectively neutralized by specific antibodies (data generated in a post-marketing study for Solvent-Detergent (SD) treated plasma).

**Strategy**
Parvovirus B19 became the first agent for which a cut-off level was established. While there has been debate on whether this limit should be $10^4$ or $10^5$ IU/ml in the manufacturing pool, the difference is not important. The important factors in these considerations are the exclusion of highly contaminated donations in context with the inactivation/removal capacities of the manufacturing process. To provide regulatory guidance the Draft chapter on viral risk assessment was prepared with the aim to outline the general principles that manufacturers should follow in performing a risk assessment with respect to potential virus transmission from plasma derived medicinal products and the basis for its evaluation by the competent authorities.

**Presentation from S. Petteway**
The case study from a manufacturer’s point of view outlined how industry manages high titer pools. Since July 2002, all PPTA member companies prepare manufacturing pools in accordance with the PPTA voluntary standard for Parvovirus B19 with a cut-off limit of $10^5$ IU Parvovirus B19 DNA per ml. Minipools that are reactive based on the targeted threshold are assessed and units are released or discarded based on individual company processes to achieve the PPTA voluntary standard. Experience has shown that the anti-Parvovirus B19 levels are not affected by this measure with 98% of manufacturing pools having a titer above 10 IU/ml. Factors in decision making:
1) Safety is context specific— the safety level of the plasma pool is only meaningful in the context of the removal/inactivation capacity of the manufacturing process;
2) Donor screen v. donation testing—the average resolution time for NAT testing ranges from 25 to 60 days. After such an amount of time the donor would have already cleared the virus and developed

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3 Eis-Hübinger et al. (1996) ZBL Bakt. 284:232-249
4 Note for guidance on assessing the risk for virus transmission – new chapter 6 of the note for guidance on plasma-derived medicinal products (CPMP/BWP/269/95) (CPMP/BWP/5180/03), London 22 October 2003.
sufficient antibodies to confer a life-long immunity by the time notification occurred. Therefore, donor notification for Parvovirus B19 is not required because it would neither be beneficial for the donor nor for public health.

Roundtable Discussion of Case
It is possible to evaluate the potential Parvovirus B19 transmission by post marketing surveillance, but it is difficult to identify Parvovirus B19 infections in recipients. It can be expected that more data becomes available over the years.

Should there be a communication with high-risk patient groups on Parvovirus B19? Parvovirus B19 is a question of quality not safety and therefore the value of a communication with high-risk patients is questionable.

In Australia only recovered plasma is fractionated. Testing is performed by fractionators, but mostly results are available after transfusion. Should blood screening be performed? It should be considered how to handle this situation.

In the patient community no real concerns were voiced regarding Parvovirus B19, but there are open questions that need to be validated.

Donor notification for Parvovirus B19 is not an issue because of the lack of consequences.

Case Study: West Nile Virus:
The outbreak of WNV in human populations in the US is a relevant case study in terms of exploring new paradigms for demonstrating blood and plasma derivative safety and considering how emerging threats to the blood and plasma supply can be anticipated. More specifically, the presence of WNV in animal populations in the US was well documented in advance of the human outbreak, yet WNV policy was not formulated until well into the human epidemic.

With respect to blood and plasma derivative safety the WNV experience points out the potential for widely varying approaches in dealing with these different blood products. While blood donor testing was instituted at an unprecedented pace, a model virus concept has been employed in an effort to demonstrate adequate viral inactivation of plasma derivatives. The use of surrogate viral models even when the virus of interest is available is a new concept that warrants examination.

Presentation from J. Epstein
In 2002 the United States was faced with an unprecedented epidemic of WNV experiencing the largest known human outbreak of WNV to date. The first case study on WNV discussed the US decision making process on WNV. The initial efforts in blood safety focused on investigation of suspected transmission and subsequently focused on risk estimation. Risk modeling was performed and a number of preventive measures to address blood safety for WNV were implemented in 2002 and 2003. Efforts are continuing to model and address transfusion risk of WNV. A distinction was made between risks
from plasma derivatives vs. blood components because of the removal/inactivation capacity of the manufacturing process for plasma derived medicinal products. The current approaches for viral clearance studies in human blood derived products include the requirement for at least two orthogonal and effective steps for removal/inactivation of viruses. The validation of these steps should be performed using the actual virus of concern if technically feasible; if not, specific model viruses can be used. The evaluation of historical and specific WNV clearance data demonstrated that certain common inactivation methodologies consistently provide significant levels of inactivation for WNV. The level of WNV inactivation is comparable to that of BVDV, a historical model for HCV. BVDV inactivation data can be extrapolated to WNV for S/D or heat treatment. But not every product has been studied with WNV and assessments have to be extrapolated from available data. J. Epstein presented FDA’s point of view to investigate WNV removal at partitioning steps where the relevance of data from model viruses in respect to WNV is less clear. Further, a safety margin of $10^5$ was suggested. A $10^{10}$ clearance factor is achieved for a number of model viruses including flaviviruses although a higher variability is observed. From the U.S. experience of implementing measures to reduce risk during the human epidemic, it should be learned that the infrastructure for dealing efficiently with a spreading epidemic such as WNV ideally needs to be in place before the arrival of the virus.

Presentation from T. Kreil

From a manufacturers perspective the model virus approach is necessary, because (practical) infectivity assays are not always available and model viruses are the only access to any information. The available experience supports the usefulness of the model virus concept. The data generated on WNV support the conclusions of regulators (FDA, EMEA\(^5\)) in that it verifies that WNV behaves exactly like expected for a flavivirus. The concept of using a range of physicochemically diverse model viruses for the validation of virus reduction steps has also been verified in that the behavior of the virus of interest, WNV, has been adequately predicted. The risk assessment for WNV for plasma derived medicinal products, which was based on the available data from a PPTA collaborative study, predicts for 2003 “at risk” pools a virus load of 100 c/ml (1:250 – highest prevalence; mean virus load – 25,000 c/ml). Factors to be considered in reacting to a risk imposed by viruses include: 1) The verification of effective virus reduction by studies with the relevant virus (i.e. WNV) may be limited due to biosafety issues. During the 2002 WNV epidemic two laboratory transmitted cases were reported. Other limitations could be the availability of the virus of concern. 2) Whether a full validation of the manufacturing process is justified also needs careful considerations. 3) Introducing testing for the agent should provide meaningful improvement of safety margins, which is not the case for WNV due to the low virus titer. 4) When adding new virus reduction steps the clinical safety and efficacy should be balanced against the improved pathogen safety profile.

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\(^5\) CPMP position statement on West Nile Virus and plasma-derived medicinal products (EMEA/CPMP/BWP/3752/03/adopted), London, 25 July 2003
Roundtable Discussion of Case
For practical reasons, suitable endpoints need to be defined for the calculation of the safety margin. The target point for the safety margin to be achieved is based on the state-of-the-art of the overall virus reduction at manufacture and the time of exposure of the recipient. For lifetime exposure, a higher safety margin would be required than for a single dose exposure.

There are other heat inactivation procedures than pasteurization. The FDA has stratified heat inactivation procedures according to the step and the product.

The throughput and cost factors need to be taken into account when testing of individual donations or minipool testing is considered.

Case Study: SARS:
SARS represents a true emerging infection. When the first cases of SARS were recognized, the cause of the disease was unknown. Fortunately, the period of time between the recognition of the new disease and the identification of the causative agent was short. In the future, the time between recognition of a new disease and causative agent may be increased with the discovery of a less clearly defined agent. It is important to examine the actions taken during the period of unknown certainty about the disease and the causative agent to evaluate whether the steps taken were the most efficacious in addressing the threat to the blood and plasma supply from the unknown agent. Of particular interest are the actions taken both at the focal point of the disease and the global response to the disease.

Presentation from Q. Shen
In China where SARS is believed to have originated the government implemented a policy to address the challenge imposed by the agent. Chinese Requirements for Biologics for collection of source plasma for blood products demanded the postponement of donation for individuals with certain infectious diseases or in the areas susceptible to be prevalent of some infectious diseases considered by the anti-epidemic sectors. Human SARS immunoglobulin was prepared from plasma of convalescent patients with SARS.

Presentation from N. Dinghra
The WHO Global Outbreak Alert and Response Network is a technical collaboration of existing institutions and networks that pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance. The network provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond. On 15 March 2003, the WHO issued a global alert using the public health evidence on SARS. The media can be the source of information for the WHO and the public, and the WHO provides information to the media. In this context it is important to develop clear messages, to be transparent about the level of knowledge and to avoid assumptions. Statements should be made on internal assessments only. The impact of SARS on blood safety must be assessed against the measures in place: donor selection, testing and
elimination/removal taking into account the uncertainties that exist. The experience with SARS showed that in the world today an infectious disease in one country is a threat to all: SARS does not respect national borders. The information that was provided early helped to contain the international spread of SARS. The SARS outbreak was contained by case detection, isolation and protection. These lessons learned can be applied to other outbreak situations. Information and travel guidance can contain the international spread of an infectious disease. Unnecessary fears should be removed by education of the public. This would also reduce the negative economic impact on travel, tourism and trade due in part to discrepancy between real and perceived risk. Experts in laboratory, epidemiology and patient care can work together for the public health. Infectious disease outbreaks reveal weaknesses in public health structure, which should be reviewed to improve hospital infection control standards. Governments need to reinvest in public health and public goods. Emerging infections can be contained with high level government commitment and international collaboration if necessary, but disincentives for reporting need to be removed.

**Roundtable Discussion of Case**

What lessons were learned form the SARS epidemic and what should be done differently? Some things worked well but the lack of reporting from countries caused a lot of problems. A more open sharing and provision of information is needed. A revision of the international health regulations will bind all member states to share information.

In the US, measures established to combat anti-bioterrorism were effective against SARS.

The answer to the question whether a robust system is in place to deal with any emerging infectious diseases is **no**. If WNV or SARS had been non-enveloped viruses, there might have been a risk for transmission by plasma-derived products since the virus reduction capacity of the manufacturing process might have been limited. In case of non-enveloped viruses, the virus load in the pool needs to be controlled by testing, which is necessary but may not be sufficient. The ultimate goal should be virus reduction at manufacture. Implementation of robust non-enveloped virus reduction steps would be an optimal goal to be prepared against an emerging non-enveloped virus disease. Also the concept of model viruses is extremely important in this context. For non-enveloped viruses, it seems more difficult to predict inactivation/removal from model-viruses. Although it would be much easier to regulate, blood and plasma for fractionation cannot be separated because of the enormous economic impact. Reality has to be accepted.

**General discussion**

Following the individual presentations and in preparation for breakout sessions to focus on addressing emerging threats, it was noted that discussion should not only focus on emerging infectious diseases but also consider:

- variance of known agents
- known agents that have dramatically changed their epidemiology, e.g. WNV
✓ known agents, who’s significance has been recognized over time, e.g. Parvovirus B19
✓ bioterrorism
✓ zoonoses that might be well known agents
✓ changes in immigration pattern, e.g. Chagas

The reactions to acute crisis against background threats that may eventually cause problems have to be considered individually.

A distillation of the individual presentations and discussions of those presentations resulted in the identification of five key areas in the management of EIDs, as follows:

1) Scientific risk assessment modeling
   - Epidemiology and laboratory data, surveillance
   - Prevalence and clinical significance
   - Infectivity
   - Transmission
   - Process reduction
   - Model viruses
   - Robustness of data, measurability
   - Infrastructure recommendations as outcome of risk assessment

2) Manufacturing process, testing, viral inactivation
   - Identification and testing
   - Product specific evaluation of clearance steps
   - Dialogue with regulators

3) Communication with donors and recipients
   - Risk balancing
   - Optimal usage
   - Communicator
     - Dynamic process of communication
   - Product labeling
   - Balance between different information sources

4) Donor exclusion criteria, leads into 3)
For the afternoon discussions, the roundtable participants were divided into two breakout sessions to focus on the five key elements identified from the morning’s case study presentations. Following the breakout sessions, the roundtable reconvened to share the results of the breakout session discussions. One participant from each group reported to the roundtable.

**Break out session I: Jay Epstein, MD (report):**

Participants: T. Barrowcliffe, B. Dickens, J. Epstein, T. Kreil, Q. Shen, G. Silvester, A. Somogyi, J. Blümel (rapporteur), and C. Healey (liaison)

The discussion in the group focused mainly on the decision making process within the identified key elements and communication between the involved parties and the public community.

**Scientific Risk Assessment**

A scientific risk assessment should be the basis for any further decision. A scientific risk assessment is difficult for new viruses as causative agents for emerging infectious diseases. In such situations, only few scientific data may have been accumulated and the group felt that a proactive effort to address such gaps would be needed. It seemed further necessary to define the trigger for action; i.e. when to act in the absence of data (risk and expectations).

In any case, the scientific risk assessment should not be influenced by interests from policy and industry. Therefore, the voice of these parties and vested interests should be limited. “Independent” experts should be consulted as far as possible and the “regulators” have an important role in directing/performing this process. At any stage of the risk
assessment, an early integration and support of scientific efforts including epidemiology and laboratory data should be performed. This requires an ongoing surveillance and communication of scientific data from any involved party during the whole process.

The scientific risk assessment should be separated from policy decisions in order to avoid pre-decision and premature public assurances. However, input from public points should be sought and the risk assessment should be communicated in a global dialogue. This dialogue should consider the (global) scientific facts separated from local requirements/policies in order to find the highest feasible protection.

Manufacturing
Regulators need highly specific information on products (e.g. sourcing of plasma, manufacturing process, validation data, affected lots, distribution patterns) in order to gain a basis for appropriate decisions. This information can only be provided from industry and industry may have wide experimental expertise. It was noted that there is some inherent conflict in the sharing of specific data between industry and other parties. Representatives from industry pointed out the problem of globally sharing confidential industry data across industry and stakeholders. A conflict with patents also often argues against sharing of data. Therefore, international information and consensus on sharing agreements would be needed to facilitate an open discussion with international regulators.

Measures on control of starting materials through selection and screening of donors or plasma may have their limitations. There was a common agreement that implementation of validated robust virus clearance steps into the manufacturing process is a good way to manage product safety. However, any change in manufacturing requires regulatory acceptance in light of a potential effect on product quality/safety. This might delay implementation of steps for virus clearance. Therefore, the mechanisms to confirm products safety in light of the planned or required manufacturing changes need to be improved. A formal risk assessment should be performed on a product-specific basis. Unavoidably unsafe products might be accepted only in the specific context.

Communication
The obligation to communicate the risk assessment was accepted. However, certain problems in the communication of risk were identified. It might be difficult to express adequately the balance between benefits and risk of a specific medicinal product. Such a risk/benefit evaluation is dependent on the specific context (e.g. fatal threats). Multiple organizations should have the opportunity to express their point of view regarding the potential risks and benefits. Both, the manufacturer and regulator were considered responsible for identifying and expressing product risk on labeling of medicinal products. The healthcare providers should have the unique responsibility as interpreters of risks to their patients supporting the patient’s role in decisions.
Donor Availability
Donor exclusions on epidemiology or other risk factors may be introduced in order to reduce the risk from emerging infectious diseases. Such measures demand a balance of safety gains of deferrals against blood losses and the options (e.g. deferral on clinical symptoms vs. geographical basis) may vary significantly by locations. In any case, it was felt necessary to differentiate the risk from whole blood vs. plasma for fractionation. This should be considered at any decision on donor/plasma deferral. The problem of giving the correct messages to the excluded donors was noted.

Increasing or decreasing the size of the manufacturing plasma pool may have a divergent effect on the risk depending on the specific context. While reduced pool sizes may reduce the risk of distribution of rare contaminants to many recipients, a small pool may negatively affect the product consistency, e.g. it might be difficult to maintain a certain level of neutralizing antibodies in small pools.

Optimal Clinical Use
The global problem of inadequate use and the need of “benchmarking” (e.g. bloodless surgery for total hip vs. blood and fibrin sealant or dosing of clotting factors) was expressed. “Benchmarking” would help to evaluate the “optimal use”. However, it was noted that the “optimal use” is only appropriate in local context as the local conditions may vary widely. Whole blood issues should again be differentiated from plasma derivatives. The problem of “off label” use was further discussed regarding the competition for availability of IGIV. Studies on the practice of use were found helpful. The discussion on the “clinical use” should pay attention to the needs of high risk patients considering the critical role of scientific data and the safety margin of different product. Manufactures were considered responsible for recalls.

Break-out session 2: Albert Farrugia (report):

Participants: J. Löwer, N. Dhingra, A. Farrugia, D. Starr, R. Perry, J. Goldsmith, S. Petteway, M. Gustafson, I. von Hoegen (rapporteur), and C. Waller (liaison)

This break-out group focused on the overall framework and process for EID decision making. The key areas to be addressed to manage EIDs imply leadership, coordination and accountability. Each of these issues bears intrinsic difficulties due to the significant number of interested parties involved. Experience has shown that one of the biggest hurdles is the identification of leadership. The lack of decision makers in a crisis situation has led to a growing sense of frustration within industry and among regulatory authorities.

Plasma is global
It has to be recognized that the plasma products industry is a globally active industry and therefore EID management needs to be driven on a global basis as opposed to local management. Inconsistencies within the plasma products industry itself, because of the competitive environment, between industry and regulatory agencies, because of different
voluntary industry standards and mandatory regulatory requirements, and within the regulatory agencies themselves, which may have adopted different policies, represent significant hurdles that are difficult to overcome. In addition to the commercially driven plasma products industry there are also public systems, which operate with different perspectives.

In order to provide accountable leadership the “we” has to be defined. Regulators, commercial plasma products manufacturers, and the non-for-profit sector need to be part of the decision making process as well as patient groups and prescribing doctors represented by their international societies. Public health institutes, such as WHO and CDC can provide the necessary global framework as well as scientific support. In addition, co-operation with these institutions will provide the necessary credibility for the general public. Last but not least the legal implications associated with EIDs themselves and the actions taken by governments and manufacturers need to be taken into account.

The definition of common goals between the different interest groups taking into account manufacturing perspective, local/commercial sensitivities and marketing issues, is a mandatory step to manage EIDs on a global level. In the past, when faced with the situation of an EID, regulators and industry tended to implement the most precautionary and rigid measures, often leading to a situation of “upstaging” between them, instead of ensuring that safe products are available. This situation should be avoided, in particular since plasma products are amongst the safest available drugs, but are made less and less available.

The political dimensions and the public perception are additional variables to be taken into account. Also differences in health care systems and reimbursement schemes may be obstacles to a harmonized approach.

The responsibilities of a global leadership could either be covered by an independent group composed of the different interest groups as outlined above or be implemented into the framework of existing committees such as the International Association of Biological Safety (IABS) or the WHO Global Collaboration of Blood Safety (GCBS). It could be considered to initiate a subgroup under the auspices of the GCBS that meets more frequently than once a year. Operation within a global organization such as the WHO will help to establish credibility for the group, their initiatives and the outcomes.

The responsibilities of an EID group would mainly focus on development of policies for new EIDs. Policy making for new EIDs should rely on developed systems already in place for which strategies to react to the unknown can be developed. Best practice guidance will be helpful for manufacturers and regulators, but can also used to provide the general public with a positive message of reassurance, when communicated appropriately.

Experience has shown that communication is the key to managing the public perception effectively. The HIV trauma of the past has left the public with the belief that whole blood and plasma are not different. The public needs to be re-educated about the difference
and the safety of plasma derived medicinal products within a framework, where issues (technical vs strategic/political) need to be placed into the correct context. To achieve the goals strategic communication objectives need to be defined and should reflect the need to proceed from a static to a dynamic communication taking into account the changing environment.

Related issues to be addressed by the group would be to ensure information sharing and coordination between regulators and manufacturers on the global level. Communications should change from static to a dynamic process reflecting the development of a given situation.

**General discussion**

Consensus among participants appeared to exist around the need for a framework to address EID policy-setting with the highest priority being a process to facilitate communication and appropriate coordination among patients, regulators and industry.

The EID Roundtable will continue with the goals of improving communications globally to address the threats of EIDs and finding a forum for developing a pathway to develop a “best practices” guideline. A further roundtable meeting was agreed to be important and worthwhile.
### Annex A: Flip charts

<table>
<thead>
<tr>
<th>General Discussion</th>
<th>2. Optimal Clinical Usage of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Manufacturing</strong></td>
<td></td>
</tr>
<tr>
<td>• Identification of testing</td>
<td></td>
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<tr>
<td>• Product specific evaluations of clearance steps</td>
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<tr>
<td>• Dialogue with regulators</td>
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<tr>
<td><strong>2. Optimal Clinical Usage of Products</strong></td>
<td></td>
</tr>
<tr>
<td>• Correct usage</td>
<td></td>
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<tr>
<td>• Identify highest products</td>
<td></td>
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<tr>
<td>• Recall/replacement</td>
<td></td>
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<tr>
<td>• Importation</td>
<td></td>
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<tr>
<td>• Synthetic products</td>
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<tr>
<td><strong>3. Scientific risk assessment</strong></td>
<td></td>
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<tr>
<td>• Measurable robust</td>
<td></td>
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<tr>
<td>• Epidemiology and lab data</td>
<td></td>
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<tr>
<td>• Transmission</td>
<td></td>
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<tr>
<td>• Prevalence and clinical significance</td>
<td></td>
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<tr>
<td>• Infectivity surveillance</td>
<td></td>
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<tr>
<td>• Model virus</td>
<td></td>
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<tr>
<td>• Processing reduction</td>
<td></td>
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<tr>
<td>• Safety margin</td>
<td></td>
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<td>• Infrastructure</td>
<td></td>
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<tr>
<td><strong>4. Donor exclusion</strong></td>
<td></td>
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<tr>
<td>• Recruitment</td>
<td></td>
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<tr>
<td>• Screening</td>
<td></td>
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<tr>
<td>• Surveillance</td>
<td></td>
</tr>
<tr>
<td>• Impact on supply</td>
<td></td>
</tr>
<tr>
<td>• Differentiate blood vs. plasma</td>
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<tr>
<td><strong>5. Communication</strong></td>
<td></td>
</tr>
<tr>
<td>• Risk</td>
<td></td>
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<tr>
<td>• Risk balancing</td>
<td></td>
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<tr>
<td>• Optimal usage</td>
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<tr>
<td>• Communicator</td>
<td></td>
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<tr>
<td>• Dynamic</td>
<td></td>
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<tr>
<td>• Product labeling</td>
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</tbody>
</table>

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**Break out session I:**  
**Jay Epstein, MD (report)**  
**Food and Drug Administration**

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Primary focus on likely new viruses as EID’s</td>
<td>Problem of sharing confidential industry data across industry and stakeholders including globally.</td>
</tr>
<tr>
<td>• Proactive effort to address gaps (e.g., mfg)</td>
<td>✓ Role of patents to promote sharing</td>
</tr>
<tr>
<td>✓ Define the trigger for action – when to act in the absence of data (risk and expectations)</td>
<td>✓ Some conflict is inherent</td>
</tr>
<tr>
<td>Limit the voice of parties and vested interests (political, industry)</td>
<td>✓ International regulators need highly specific information on products (affected lots, distribution patterns)</td>
</tr>
<tr>
<td>✓ Use “independent” experts</td>
<td>✓ International information sharing agreements</td>
</tr>
<tr>
<td>✓ Special role of regulators wrt process</td>
<td>• Stepped up effort to validate and implement</td>
</tr>
<tr>
<td>✓ Early integration and support of scientific efforts including</td>
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</tbody>
</table>
## Epidemiology and Laboratory Efforts
- Surveillance “scanning” ongoing
- Separate risk assessment from policy decisions to avoid pre-decision
- Avoid premature public assurances
- Seek input from public points
- Global dialogue (facts) vs. local policies – highest feasible protection

## Surveillance “Scanning” Ongoing

## Separate Risk Assessment from Policy Decisions Per Se
- Avoid premature public assurances
- Seek input from public points
- Global dialogue (facts) vs. local policies – highest feasible protection

## Robust Clearance in Manufacturing
- Despite limits on control of starting material through selection and testing
- Formal assessment of product risk
- Improve mechanisms to confirm products safety in the face of manufacturing changes
- Unavoidably unsafe products can be accepted in context

### 3. Communication
- Obligate need to communicate
- Difficulty of communication of risk
  - Balance of benefit/risk
  - Multiple organizations should speak
  - Risk assessment is context dependent (e.g. fatal threats)
  - Unique responsibility of healthcare providers as interpreters patients role in decisions
- Responsibility of the manufacturer and regulator to identify product risks
  - Labeling

### 4. Donor Availability
- Base donor exclusions on epidemiology/risk factors
  - Options vary by location e.g. symptom vs. geographical based deferrals.
  - Balance safety gains of deferrals against blood losses
  - Differentiate whole blood vs. plasma for fractionation
- Uncertain role of pool size in increasing or decreasing risk
  - Risk of contamination
  - Product consistency e.g. NtAb
- Messages to the donor

### 5. Optimal Clinical Use
- Manufacturers responsible for recalls
- Global problem of inadequate use e.g. clotting factors
- Value of “benchmarking” e.g. bloodless surgery for total hip vs. blood and fibrin sealant; CF dosing
- Whole blood issues may differ from derivatives
- “Optimal use” is only appropriate in local context
- Problem of off-label use
  - Competition for availability of IGIV
  - Role of practice studies utilization controls
- Attention to needs of high risk patients
  - Critical role of scientific data
  - Margin of safety for different products
### Break out session 2:
Albert Farrugia, MD (report)
Australian Therapeutics Goods Association

<table>
<thead>
<tr>
<th><strong>Plasma is Global</strong></th>
<th><strong>Responsibilities</strong></th>
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</thead>
<tbody>
<tr>
<td>Issues</td>
<td>Policies for new EIDs</td>
</tr>
<tr>
<td>Politics</td>
<td>Best practice guide for EIDs: risk assessment</td>
</tr>
<tr>
<td>Public perception</td>
<td>Definition of comms objectives</td>
</tr>
<tr>
<td>Healthcare systems</td>
<td>Obviate ambiguity: Policies IABS, GCBS - subgroup</td>
</tr>
<tr>
<td>Manufacturers and regulators up-staging authorities</td>
<td></td>
</tr>
<tr>
<td>Defining the “we”</td>
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<tr>
<td>Manufacturers: plasma industry, not for profit</td>
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<tr>
<td>Regulators</td>
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<tr>
<td>Patient groups</td>
<td></td>
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<tr>
<td>Public Health Institutes: WHO, CDC, Regional health authorities</td>
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<tr>
<td>Prescribing Doctors</td>
<td></td>
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<tr>
<td>Legal</td>
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</table>

<table>
<thead>
<tr>
<th><strong>Related Issues</strong></th>
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<tbody>
<tr>
<td>- Need for Regulators to share information and co-ordinate</td>
</tr>
<tr>
<td>✓ ICH does not cover blood and plasma</td>
</tr>
<tr>
<td>- Manufacturers to co-ordinate better</td>
</tr>
<tr>
<td>- Communications – static to dynamic “Blood bank - blood pipeline”</td>
</tr>
</tbody>
</table>
Annex B: Participants

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Medicus International
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Jay Epstein, MD: Presenter – WNV
Director
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Center for Biologics Evaluation and Research
Food and Drug Administration (FDA)
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Immune Deficiency Foundation
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Director, Global Pathogen Safety
Baxter Bioscience
Austria

Professor Johannes Löwer, MD: Presenter – Parvo B19
President
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Director
Protein Fractionation Centre
Scottish National Blood Transfusion Service
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Plasma Protein Therapeutics Association
Annex C: Presentations
U.S. Decision Making on West Nile Virus (WNV)

EID Roundtable
11 March 2004

Jay S. Epstein, M.D.
Office of Blood Research and Review
CBER, FDA
U.S. Decision Making on WNV

- Background on WNV
- Investigations in 2002
- Actions in 2002 and 2003
- Current thinking on insuring safety of plasma derivatives
Background Information on WNV

• WNV is a flavivirus, distantly related to hepatitis C virus
  – It is enveloped, and contains single stranded RNA
  – It is spread by the bite of several species of mosquito
  – It primarily infects birds, but occasionally infects humans and other incidental animal hosts
• About 80% of human infections are asymptomatic, however
  – 20% develop a mild febrile, flu-like illness
  – Approximately 1 in 150 infections results in meningitis or encephalitis that can be fatal; polio-like illness also occurs
  – Advanced age is a significant risk factor for severe neurologic disease
• A viremic period can occur up to 2 weeks prior to symptoms and last up to a month following infection
Investigation of the Epidemiology of WNV in the US During the 2002 Epidemic

- Largest known human outbreak of WNV to date
  - 4156 human cases reported, including 2942 cases of meningoencephalitis and 284 deaths between May-Dec.

- Initial efforts in blood safety focused on investigation of suspected transmissions
  - 61 possible transfusion-transmitted cases were reported and 23 were confirmed from 6 implicated blood donations (NEJM 2003; 349:1236)

- Subsequent efforts focused on risk estimation
  - Based on a model developed in 1999, the average risk of WNV by transfusion nationwide was estimated to be 4 per 100,000 donations, with a maximum risk of 105/100,000 donations
Preventive Measures to Address Blood Safety for WNV in 2002 and 2003

• A recurrent WNV epidemic in 2003 was predicted. To address this possibility:
  – An intensive effort was begun to develop screening tests through government and industry cooperation.
  – FDA issued Guidance in October 2002 on vigilance in deferral of symptomatic donors, investigation of suspect cases and management of potentially affected products. Plasma derivatives were presumed to be safe based on the nature of the virus and the expectation of inactivation in processing.
  – FDA encouraged blood organizations to replace units of FFP that had been collected in the epidemic period with units collected at a later time.
Preventive Measures to Address Blood Safety for WNV in 2002 and 2003, cntd.

• CDC performed an analysis of symptoms in donors and the American National Red Cross estimated impact of a new deferral. Based on this:
  – In May 2003 FDA recommended deferral of persons with fever+headache in the week prior to donation

• FDA approved nationwide investigations of two screening tests for WNV using nucleic acid detection in small “minipools.”
  – Donor screening began in mid June 2003 and encompassed 95% of whole blood collections by 1 July.
  – Testing was not implemented by collectors of Source Plasma based on a presumption of plasma derivative safety. However, FDA called for safety validation.
Outcome of WNV Epidemic in 2003

- A highly coordinated program of surveillance was established in 1999 (ArboNet) and expanded in 2002.
- 9,122 symptomatic cases of WNV (69% WNV fever and 30% WNM&E) have been reported in 2003, including 223 deaths. Serological testing has increased reporting.
- **Donor screening removed over 1,000 positive donations**
  - More than 6 million donations were tested
  - Individual unit testing was performed in areas of highest risk
  - The last positive donation occurred in mid-December
- CDC has investigated 23 possible transfusion cases:
  - 6 probable/confirmed (2 reported in MMWR, 26 Sept. ’04)
  - 5 investigations are still open
Model for Relative Duration of Stages of WNV Infection

Stage-I
IDNAT+/-
MPNAT-
IgM-

Stage-II
IDNAT+
MPNAT-
IgM-

Stage-III
MPNAT+
IgM-

Stage-IV
IDNAT+
MPNAT-
IgM+
IgG+/-

Stage-V
IDNAT +/-
MPNAT-
IgM+
IgG+

Days post infectious mosquito bite

WNV RNA (gEq per mL)

6-7 days

IgM

IgG

MP-NAT

ID-NAT
Continuing Efforts to Model and Address Transfusion Risk of WNV

- Retrospective individual unit testing of “minipool” negative units from high incidence areas has suggested that screening with “minipools” was about 75% sensitive to detect viremic donations.
- Low titer viremic blood samples (both IgM negative and IgM positive) missed by “minipool” screening will be inoculated into primates to determine their likely infectivity.
- FDA is developing reference reagents to ensure sensitivity of WNV screening tests.
- Industry is planning earlier use of individual unit testing in high incidence areas in 2004.
Current Approach for Viral Clearance Studies in Human Blood Derived Products

- Manufacturing processes must contain at least two orthogonal and effective steps for removal/inactivation of viruses. Effective is defined as achieving > 4 log clearance.

- One of the clearance steps must be inactivation

- The validated steps should remove/inactivate three to five orders of magnitude more virus than is estimated to be present in the starting materials (for enveloped viruses this is estimated to be ≥10 log total reduction)

- The actual virus of concern should be used in viral validation studies if technically feasible.

- Specific model viruses can be used in validation studies if technical/ experimental limitations do not allow use of the relevant virus.
Questions with Regard to WNV

1. Are viral validation data on model flaviviruses sufficient to demonstrate WNV clearance?

2. Do the clearance steps in the manufacture of plasma derivatives obviate the need to screen donations of source plasma?
Evaluation of Historical and Specific WNV Clearance Data

- FDA has reviewed the viral reduction processes in place for all plasma derivatives, which have been validated to inactivate enveloped viruses and flaviviruses related to WNV.

- FDA has reviewed WNV specific verification data generated by plasma industry, comparing WNV inactivation to related viruses.
# Susceptibilities of Enveloped Viruses To Inactivation

<table>
<thead>
<tr>
<th>Virus</th>
<th>Pasteurization</th>
<th>Solvent/Detergent</th>
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</thead>
<tbody>
<tr>
<td>BVDV</td>
<td>Pesti</td>
<td>≥ 5.0</td>
</tr>
<tr>
<td>TBEV</td>
<td>Flavi</td>
<td>≥ 7.3</td>
</tr>
<tr>
<td>YFV</td>
<td>Flavi</td>
<td>≥ 5.9</td>
</tr>
<tr>
<td>VEE</td>
<td>Alpha</td>
<td></td>
</tr>
<tr>
<td>Sindbis</td>
<td>Alpha</td>
<td>≥ 7.8</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Retro</td>
<td>≥ 6.0</td>
</tr>
<tr>
<td>HIV-2</td>
<td>Retro</td>
<td>≥ 7.8</td>
</tr>
<tr>
<td>HSV-1</td>
<td>Herpes</td>
<td>≥ 6.3</td>
</tr>
<tr>
<td>PRV</td>
<td>Herpes</td>
<td>≥ 4.8</td>
</tr>
<tr>
<td>CMV</td>
<td>Herpes</td>
<td></td>
</tr>
<tr>
<td>Vaccinia</td>
<td>Pox</td>
<td>≥ 5.8</td>
</tr>
<tr>
<td>VSV</td>
<td>Rhabdo</td>
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<tr>
<td>Sendai</td>
<td>Paramyxovirus</td>
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<tr>
<td>DHBV</td>
<td>Hepadna</td>
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</table>
Susceptibilities of WNV Related Viruses To Inactivation

<table>
<thead>
<tr>
<th>Virus</th>
<th>Type</th>
<th>Pasteurization</th>
<th>Solvent/Detergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMDV</td>
<td>Pesti</td>
<td>$\geq 5.0$</td>
<td>$\geq 4.2$</td>
</tr>
<tr>
<td>TBEV</td>
<td>Flavi</td>
<td>$\geq 7.3$</td>
<td></td>
</tr>
<tr>
<td>YFV</td>
<td>Flavi</td>
<td>$\geq 5.9$</td>
<td></td>
</tr>
<tr>
<td>VEE</td>
<td>Alpha</td>
<td>$\geq 6.0$</td>
<td></td>
</tr>
<tr>
<td>Sindbis</td>
<td>Alpha</td>
<td>$\geq 7.8$</td>
<td>$\geq 6.5$</td>
</tr>
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</table>
### Comparison of WNV and BVDV Clearance by Common Methodologies

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Virus</th>
<th>Heat Treatment*</th>
<th>S/D</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>α-1 PI</td>
<td>rF VIII</td>
</tr>
<tr>
<td>1</td>
<td>WNV</td>
<td>≥ 6.4</td>
<td>≥ 7.2</td>
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<td></td>
<td>BVDV</td>
<td>≥ 4.8</td>
<td>≥ 5.9</td>
</tr>
<tr>
<td>2</td>
<td>WNV</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>BVDV</td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>WNV</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BVDV</td>
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</tbody>
</table>

Source: Data Submitted to CBER by 3 Manufacturers of Plasma derived products

* Pasteurization or vapor heat
### Evaluation of WNV Clearance Data

1. Certain common inactivation methodologies (S/D and heat) that have been used by multiple manufacturers in multiple products, consistently provide significant levels of inactivation (>5 logs) for WNV.

2. The level of WNV inactivation is comparable to that of BVDV, an historical model for HCV.
Current Thinking with Respect to WNV Clearance

• Available viral clearance data, comparing WNV to BVDV, have demonstrated comparable levels of clearance for these viruses following S/D or heat treatment in multiple products.

• BVDV inactivation data can be extrapolated to WNV for the aforementioned methodologies.
• The level of inactivation shown in these studies, combined with the expected (but not yet determined) contribution of the removal steps in the manufacturing processes, are expected to be sufficient to demonstrate the safety of plasma derivatives with regard to WNV.

• Validation data with regard to removal steps, comparing WNV clearance to model flaviviruses, are needed to further establish WNV safety of plasma-derived products.
• FDA is requesting that manufacturers document the adequacy of clearance steps for all their products with respect to WNV using:

  – WNV or BVDV data for well established clearance steps (S/D and heat)

  – WNV data for novel or less established clearance steps
Summary of Decision Making on WNV

• In 2002 the U.S. was faced with an unprecedented epidemic of WNV

• Intensive investigations established transfusion-transmission

• Risk modeling was used to guide interventions
  – Donor deferrals were recommended despite an expectation of limited effectiveness
  – Sensitive donor screening was implemented rapidly under approved investigation protocols

• A distinction was made between risks from plasma derivatives vs. blood components
  – Validation of plasma derivative safety is ongoing

• Risk assessments are being updated
West Nile Virus

Thomas R. Kreil, Ph.D.
Global Pathogen Safety, Director
Baxter BioScience

Emerging Infectious Diseases Roundtable
Brussels / March 11, 2004
The model virus approach

Why are model viruses necessary?

- HIV, **HBV**, **HCV**: relevant viruses
- HAV, **B19**: non-enveloped viruses, more recent concern

→ Not always (practical) infectivity assays available: model viruses the only access to any information

→ Available experience does support the usefulness of the model virus concept
Model viruses *

• ... resemble viruses which could contaminate ...

• ... represent a **wide range** of physico-chemical properties ... eliminate viruses **in general**.

• ... laboratory strains ... any virus used in a validation study is actually **a model virus**.

• ... have been contaminated by HIV. ... **must be** evaluated

* CPMP/BWP/268/95, NfG for Virus Validation Studies
The model virus approach

**Summary**

- The use of model viruses is inherent to studies
- History: supports the model virus concept
- Specific risk requires specific action ... (e.g. HIV)

→ **NEW** concerns: **verification** of assumptions ...
West Nile Virus, WNV

- 1937: isolated from the blood (!) of a febrile woman, West Nile district of Uganda

- 2002 & 2003: epidemics of unprecedented size in the US
  - 4156 and 9306 human cases reported to CDC / Arbonet, including 284 and 240 human fatalities
  - Virus transmission through blood transfusion (MMWR [2002] 51(39): 879)
  - Laboratory acquired (2 cases: MMWR [2002] 51 (50): 1133)
  - Solid organ transplantation, breast milk (MMWR [2002] 51: 877 ff)
West Nile Virus, WNV

• Transmission of WNV through blood transfusion in the US in 2002 *

  – 16 donors → 23 (clinically) infected recipients
    • red cells, platelets, FFP: → LABILE blood products
    • plasma products: → NOT implicated

  – Implicated donations
    • plasma viremia: 0.8 - 75 pfu/ml
    • donors negative for WNV IgM
    • many asymptomatic prior to / after donation

* Pealer et al. NEJM [2003] 349: 1236
West Nile Virus, WNV

- FDA / Final Guidance for Industry (October 25, 2002)
  - Recommendations for the Assessment of Donor Suitability and Blood and Blood Product Safety in Cases of Known or Suspected West Nile Virus Infection

*FDA has reviewed the viral reduction processes in place for all plasma derivatives. The methods in place have been validated to inactivate flaviviruses related to WNV.*

→ „MODEL VIRUSES“
West Nile Virus, and relatives / Flaviviridae

• Flavivirus
  – West Nile Virus (WNV)
  – St. Louis encephalitis virus (SLEV)
    • US 1975: 1,800 clinical cases, 130 fatalities (recent years: ??)
  – Tick-borne encephalitis virus (TBEV)
    • Austria (only 8 mio.): up to 600 cases per year, 2% lethality

• Pestivirus
  – Bovine viral diarrhea virus (BVDV)

• Hepacivirus: Hepatitis C virus, HCV
West Nile Virus, and relatives / *model* viruses

Pasteurization of Human Albumin

![Graph showing the pasteurization of human albumin with various viruses at different incubation times.](image)

- **BVDV 3.5%**
- **BVDV 25%**
- **TBEV 3.5%**
- **TBEV 25%**
- **SINV 25%**
- **WNV 3.5%**
- **WNV 25%**

The graph shows the logarithm of TCID50/ml against the incubation time at 60°C in minutes. The limit of detection for BVDV is indicated. The data is from TR Kreil et al, Transfusion [2003] 43: 1023.
West Nile Virus, just another Flavivirus

• The WNV data generated support the conclusion of regulators (FDA, EMEA), in that it verifies that WNV behaves exactly like expected for a flaviviruses.

• The concept of using a range of physicochemically diverse model viruses for the validation of virus reduction steps has also been verified, in that the behaviour of a virus of interest, i.e. WNV, has been adequately predicted!
And the next Flavivirus?

H. Weissenböck et al.
EID, Vol.8/7, July 2002

„Emergence of **Usutu virus**, an African Mosquito-Borne Flavivirus of the JEV Group, in Central Europe“

**Model virus data are valid for all these closely related viruses!**
Risk assessment: How much risk is a risk?

- Plasma viremia?
- Plasma manufacturing pool loads?
  - Infectious virus titer of positive units?
  - Prevalence of viremia in the donor population?
- Reduction by manufacturing processes?
- Further relevant features?
  - Feasibility / efficacy of testing
  - Acute vs. chronic infection
  - Clinical significance of infection
Risk assessment: How much risk is a risk?

→ WNV, for example

• Plasma viremia? → YES

• Plasma manufacturing pool loads? → ???
  – Infectious virus titer of positive units?
  – Prevalence of viremia in the donor population?

• Reduction by manufacturing processes? → YES

• Further relevant features?
  – Feasibility / efficacy of testing
  – Acute vs. chronic infection
  – Clinical significance of infection
Risk assessment: WNV, for example

• Plasma viremia, **maximum**
  – 2002 (NGI): 200,000 copies / ml
  – 2003 (ARC): 390,000 copies / ml

• Prevalence of viremia in the donor population, **maximum**
  – 2002 (CDC & ARC): 1:1,000
  – 2003 (ARC): 1:250 (limited areas)

• **Worst Case**, i.e. highest load & highest prevalence:
  – 2002: 200 copies / ml
  – 2003: 1,700 copies / ml
Risk assessment: WNV, for example

• PPTA Cooperative Study
  – Samples: 50 plasma manufacturing pool retention samples per company, **targeted for WNV risk**
    • Time: collections from August 20 to September 22, 2002
    • Area: IL, MI, OH, LA, IN, TX, MS, MO, and NE
  – Collectively represented > 1 million donations
  – Negative and positive controls
    • Plasma free of WNV, and plasma spiked with WNV
  – Freeze-thaw control study
Risk assessment: WNV, for example

- PPTA Cooperative Study
  
  - 93% at or below 100 copies/ml
    
    - 70.5% negative (both tests), LOD – 16 c/ml
    - 17% qualitatively positive, but below 100 copies/ml
    - 5.5% at 100 copies/ml
  
  - 7% at more than 100 copies/ml: range 200-420 copies/ml
    
    - Blinded controls tested as expected

- Assay-based mean: 40 c/ml

- Prediction for 2003 „at risk“ pools: 100 c/ml
Risk assessment: WNV, for example

Further relevant features

• **Testing:** no meaningful enhancement of safety margins
  – Pools selected for **maximum** risk ~ LOD for current tests

• **Acute** infection: donor deferral desired for 4 weeks only
  – Thereafter: valueable contribution of antibodies!

• **Clinical** significance: only 1 in 150 cases
  – Immuno-compromised patients: antibody content of products ??
How does one react to which risk?

• Verification of effective virus reduction
  – Biosafety issues: operator safety, availability?

• Full validation of manufacturing processes

• Introduce testing for the agent
  – Meaningful improvement of safety margins, vs. addtnl. cost?
  – New tests for every flavivirus „of concern“?

• Addition of new virus reduction steps
  – Clinical safety & efficacay, vs. improved pathogen safety profile
How does one react to which risk?

- **WNV, for example**
  - Transfusion-transmission realized (during 2002)
  - Experimentally available (although BSL-3 !)
  - Clinical consequences: relatively rare
  - Virus titers in plasma: low

→ Verification of high safety margins,
   also using the „agent of concern“
→ Due to low titers: testing of insignificant value
Thank you!
SARS – backups
Severe Acute Respiratory Syndrome, SARS

- Worldwide distribution
- Very rapid spread
- 2003 outbreak:
  - 8422 infections
  - 9% lethality
SARS

- Coronavirus
  - isolated on Vero cells
  - spherical, 120-160 nm
  - lipid enveloped
  - ss linear RNA, 27-31 kb
  - short pre-clinical incubation period

- SM Poutanen et al.
  NEJM, March 31, 2003
SARS

• “FFM-ic“ coronavirus
  (Frankfurt am Main index case)

  – **190 copies/ml in plasma**
    • PCR positive only after U/C
    • Clinical disease
    • Only 1/3 patients

  • C Drosten et al.
    NEJM, April 10, 2003
SARS

• Safety of Plasma Derivatives
  
  – Lipid-envelope: expected sensitivity to SD
  – Known heat-sensitivity of coronaviruses
    
    
    
SARS: coronavirus model

Inactivation of Coronavirus (Mouse Hepatitis Virus) by Pasteurization

- log_{10} [TCID_{50}/ml]
- incubation at 60°C [min]
- albumin 5%
- PBS w/stab.

Limit of detection
SARS: coronavirus model

Inactivation of Coronavirus (Mouse Hepatitis Virus) by Vapor Heating

*...mean of 2 studies
**...mean of 3 studies
How does one react to which risk?

• **SARS, for example**
  – Known occurrence in blood (during *clinical* disease)
  – Transfusion-transmission *not* demonstrated
  – Experimentally available (**aerosol-transmitted** BSL-3 !!)
  – Clinical consequences: more frequent
  – Virus titers in plasma: (very) low

→ Verification of safety margins, using a closely related model virus!
→ Further steps?
How does one react to which risk?

- **Decision Matrix**
  - Known occurrence in blood
  - Epidemiology (Distribution, Spread ...)
  - Transfusion-transmission: possible, demonstrated, by products ..
  - Experimental features: availability (agent & assay), BSL, information about the virus / closely related models ...
  - Clinical consequences: for donor & recipient, acute vs. chronic infection
  - Physicochemical features: lipid envelope, resistance
  - Biological properties: transmission routes, viremia ...
The Longer Term “Big Picture”:
Getting ahead of the curve, anticipating new threats

kindly provided by Dr. Donald Baker
Blood Products Safety In China

Division of Blood Products, The National Institute of the Control of Pharmaceutical and Biological Products, Beijing, China
Blood Products Safety In China

- Blood products overview in China
- Policy for emerging infectious diseases presenting to the safety of plasma therapeutics in China
Blood products overview in China

- 36 plasma fractionation facilities in China, operating either in China national blood production corporation, or local provincial governments, or joint venture.

- They are licensed and regulated under the State Food and Drug Administration in China (SFDA)
Blood products overview in China

- GMP were introduced into China in 1998. All of 36 manufacturers passed.
- Theoretical design capacity per year is approximately 8000 tons source plasma for blood products in China, real production is 4000 tons. There is the increasing tendency.
Plasma for blood products

![Graph showing plasma production in tons from 2001 to 2003]
Risk Reduction is the Result of Combined Measures

Donor → Donation Management

Screening

Donor → Donor

Postmarketed surveillance

Donor → Patient

Testing → Inventory management

Testing → Plasma pooling testing

Donation Management → Manufacturing

QA、GMP

Viral removal/inactivation

Lot release → Complete Manufacture
Plasmapheresis centers

- Around 150 plasmapheresis centers for collection of source plasma for blood products are strategically located throughout China.

- They are licensed and administrated under the Ministry of Health through the Dept. of Medical Policy and local Health Dept.
Requirements for biologics

- Under the SFDA, National Institute for the Control of Pharmaceutical and Biological Products, the Committee for Standardization of Biologics are responsible for setting standards for QA and QC for blood products.

- Our Institute provides technological support of products safety and efficacy for SFDA.
Plasmapheresis centers

- Strict criteria is much needed for effort to improve safety and control HIV and HCV transmission. Standard for plasma collection centers issued by the Ministry of Health
- Licensed plasma collection centers
- Banned manual plasma collection, all by plasmapheresis since 1997
- All donors were immunized with licensed HBsAg vaccine based on the high incidence of HBsAg positive
Procedures for plasma collection

New donor and Registered donor

- Donor identity
  - YES
    - Physical examination
      - YES
        - Elimination
        - Sera tests
          - YES
            - Plasma positive treatment
          - NO
            - Lab. testing
              - YES
                - Production
              - NO
                  - NO
          - NO
            - Elimination
      - NO
        - Elimination
  - NO
    - Elimination

- Health-inquiring
  - YES
    - Sera tests
      - YES
        - Plasma positive treatment
      - NO
        - Lab. testing
  - NO
    - Elimination
Testing for source plasma

- Main tests before donation (plasmapheresis center)
  HBsAg, Anti-HCV, Anti-HIV, ALT and syphilis
- Main tests after donation (manufacture)
  HBsAg, Anti-HCV, Anti-HIV, ALT and syphilis
- Minor pooling (some manufacturers)
  HBsAg, Anti-HCV and Anti-HIV
  NAT testing for HCV and HIV
Performing virus inactivation of plasma derivatives in China

- The National Control Authority required a virus removal/inactivation step must be included in the plasma derivatives manufacturing in 1995.
- Since that time, all plasma derivatives produced in China have be performed virus removal/inactivation in their manufacturing process.
- The safety and quality of plasma derivatives have improved significantly in recent years.
The methods used for virus removal/inactivation of plasma derivatives in China

- Pasteurization
- pH4 incubation
- S/D treatment
- Nanofiltration
- Heating of dry
The methods used for virus removal/inactivation of plasma derivatives in China

- Human albumin
  Pasteurization
- IgG
  Pasteurization, pH4 incubation, S/D treatment, Nanofiltration
- Coagulation factors (FVIII, PCC, fibrinogen, fibrin sealant, Thrombin)
  S/D treatment, Nanofiltration, Heating of dry
- Plasma
  S/D treatment
Lot release for albumin

- The National Control Authority required Lot release for 6 kinds of biologics including albumin in 2002 referring to WHO relevant documents
- NICPBP and 7 provincial institute for drug control are authorized to implement Lot release for albumin
- Including lab. testing and data check
Main blood products

- The main products are as follows:
  - Human albumin
  - Human immunoglobulin for intramuscular
  - Human immunoglobulin for intravenous (pH4)
  - Human immunoglobulin for intravenous
  - Human hepatitis B immunoglobulin
Main blood products

- Human tetanus immunoglobulin
- Human rabies immunoglobulin
- Human coagulation factor VIII
- Human prothrombin complex
- Human fibrinogen
- Human fibrin sealant
- Human thrombin
Policy for SARS

- Chinese Requirements for Biologics for collection of source plasma for blood products demanded that postponement of donation for individuals with certain infectious diseases or in the areas susceptible to be prevalent of some infectious diseases considered by the anti-epidemic sectors.

- Preparing Human SARS immunoglobulin using of plasma from convalescent patients with SARS.
Policy for vCJD

- vCJD is now not observed in China
- Policy for vCJD was implemented in July, 2002
- Banned import blood products manufactured from plasma collected in the Nations with the epidemic of CJD
- Banned import other biologics presenting human albumin as stabilizer manufactured from plasma collected in the Nations with the epidemic of CJD
Policy for vCJD

- The 20 Nations with the epidemic of CJD include Britain, Netherlands, Denmark, Germany, Belgium, Spain, Ireland, Austria, Portugal, Italy, France, Finland, Greece, Switzerland, Japan, Luxembourg, Czecho, Slovakia, Liechtenstein and Oman
Policy for import blood products

- All blood products except Human albumin have been banned to imported into China since 1985 according to no. 49 document of Chinese Ministry of Health
- The decision was made to prevent HIV
THANK YOU
vCJD

Sol Ruiz

Brussels, March 11, 2004
EMEA Expert Workshop on Human TSEs and Medicinal Products
19-21 June 2002

**Objectives**

- review the latest information on human TSEs
- review precautionary measures in place; additional measures?
- harmonization between EU member states

**Topics**

- epidemiological data and risk factors, distribution of infectivity, review of screening tests, initiatives on standardization, leucodepletion, removal and partitioning during the manufacturing process

**Participants**

TSE expert group, members of the BWP, BPWG and CPMP, experts in the field, representatives from the manufacturers, EC and patient’s asscns.
Blood transfusion linked to vCJD death

The death of a man in the UK who had received blood from a donor incubating variant Creutzfeldt-Jakob disease (vCJD) is the first case of "possible transmission" of the disease in blood. The man, who died from vCJD in autumn 2003, had been given blood in 1998 from an apparently healthy donor who developed the disease 3 years later and died.

The transfusion took place before the introduction of precautions against the unknown risk of vCJD, such as leukodepletion and the sourcing of plasma from the USA, instead of the UK. Since 1997, blood donation records of all cases of "probable vCJD" diagnosed by the UK National CJD Surveillance Unit have been checked and any identified blood stocks destroyed. All 15 patients who received blood from people who subsequently developed vCJD (ten before leukodepletion was introduced) have been contacted.

First US case of BSE
On Dec 23, 2003, the first case of bovine spongiform encephalopathy (BSE) in the USA was confirmed in a cow slaughtered on Dec 9. The animal, from a farm in Washington state, was one of a herd of 82 cows imported in 2001 from Canada, where a case of BSE was confirmed in May 2003. The cow, aged 6 years when slaughtered, would have been born before feed bans were implemented in North America (in August 1997). In the UK, BSE has been transmitted to human beings through consumption of infected beef products, causing variant Creutzfeldt-Jakob disease.

There is no test to detect the vCJD prion in blood, so donated blood cannot be screened for the infective agent. The UK National Blood Service says, "It is important to balance the unknown risk of contracting vCJD through a blood transfusion against the risk of a patient not receiving the blood transfusion they require".

In October 2003 the Advisory Committee on the Microbiological Safety of Blood and Tissues advised the UK government that excluding blood-transfusion recipients from donating blood "would have a damaging effect on blood supplies". UK Health Secretary John Reid has asked the committee to consider what further precautionary measures could be taken without adversely affecting the safety and supply of blood. Regional and hypertensive anaesthetic techniques, salvage, and reinfusion of red cells lost during surgery, and the use of antifibrinolytic drugs are being increasingly used to reduce reliance on transfusion. Some experts predicted a huge epidemic of vCJD, but so far only 143 cases have been identified in the UK, and the number of new cases has fallen in each of the past 3 years.

Dorothy Bonn
Issues for discussion

- epidemiological review of vCJD, predictions of future number of cases, testing of tissue samples

- the case of possible transmission by blood transfusion

- review of results of studies of infectivity in blood of animals, including transfusion experiments, and investigations of the effect of leucodepletion
EMEA Expert Workshop on Human TSEs and Medicinal Products, January 2004

Issues for discussion

- full review of investigations relevant to the removal of infectivity by manufacturing processes for PDMP including both studies with endogenous infectivity in animal blood and spiking studies

- CPMP Discussion Paper

- sanitization of equipment in relationship to the CPMP Discussion Paper

- risk assessments in relation to vCJD and PDMP
Residence in the UK recognized as a risk factor for vCJD. UK stopped using their own plasma for fractionation (1998)

Some EU member states introduced exclusion of donors based on cumulative period of time spent in the UK

CPMP Position Statement on CJD and plasma-derived and urine derived medicinal products (February 2003)
Recommendations and proposals

recall policy

donor exclusion criteria

manufacturing process
CJD & Plasma-derived products

recall policy

No change to the previous CPMP position i.e. recall of plasma-derived medicinal products is not justified where a donor is later confirmed as having sporadic, familial or iatrogenic CJD

Recommendations and proposals February 2003- January 2004
As a precautionary measure, batches of PDMP should be recalled where a donor to a plasma pool subsequently develops vCJD, including medicinal products containing PDMP as excipients.
It is recommended that donors who have spent a cumulative period of one year or more in the UK between the beginning of 1980 and the end of 1996 are excluded from donating blood/plasma for fractionation.
Country based donor exclusions

Risk factors:
✓ time spent in the UK
✓ endogenous risk (BSE incidence/imports)

POLICIES IN THE EU MEMBER STATES

- no exclusion: Denmark, Netherlands, Sweden, Norway
- five years: Ireland
- one year: France, Spain, Luxembourg (?)
- six months: Austria, Belgium, Finland, Germany, Greece, Italy, Portugal
Manufacturing process for PDMP

- It is still unknown to what extent infectivity may be present in human blood in the preclinical phase of the disease.
- Experimental data from animal models suggest a low level of infectivity (blood and blood components).
- Data from investigational studies support the removal of infectivity by steps commonly used in the manufacture of PDMP; effectiveness dependent on a number of variables.

✓ *Stenland et al.* Transfusion (2002)
✓ *Vey et al.* Biologicals (2002)
It is recommended that manufacturers use this general information to evaluate the potential of key steps of their specific manufacturing processes to reduce infectivity.
It is also highly desirable that manufacturers undertake product-specific evaluation on key steps for PDMP as a precautionary measure.

CPMP’s Biotechnology Working Party, with the involvement of external experts, will develop a “Points to Consider” document to provide guidance on this respect.
CPMP Position Statement
on CJD and Plasma-derived and urine-derived medicinal products, January 2004

- No change to the previous CPMP position on recall of PDMP
- Available data indicate that the manufacturing process for PDMP would reduce infectivity if it were present in human plasma. Manufacturers are now required to use this general information to analyze the potential of their manufacturing processes to reduce infectivity
- It is also recommended that manufacturers undertake product-specific investigational studies on key steps for PDMP
- CPMP’s BWP is developing a Points to Consider document
Case Study: Parvovirus B19

EID Roundtable, Brussels, 11 March 2004

Johannes Löwer
Johannes Blümel

Paul-Ehrlich-Institut (PEI)
www.pei.de
Parvovirus B19 (B19V) infection

### Clinical Manifestations

1. Erythema infectiosum (Fifth Disease)

2. Polyarthralgia, Arthritis

3 (severe) transient aplastic crises *(patients mit erythropoietic disorders)*

4. Pure Red Cell Aplasia *(immunosuppressed Patients)*

5. Hydrops fetalis, congenitale anaemia *(pregnant women and newborns)*

6. Sporadic reports of myocarditis, vasculitis, glomerulonephritis pneumonia, encephalitis.

**Therapy:**
- erythrocyte concentrates
- immunoglobulins
Parvovirus B19 and Plasma-Derived Medicinal Products

- viraemic donors are assymptomatic
- frequency of viraemic donors: 1:800 to 1:8000 (highly viraemic)$^1$
- very high virus concentration in viraemic plasma donations (up to $10^{12}$ genomes per ml)
- Parvoviruses are small non-enveloped viruses which are difficult to inactivate/remove during production.

These factors confer to the risk of B19V transmission via plasma-derived medicinal products.

Detection of B19 DNA in Plasmapools (PEI results)

222 of 372 pools B19-DNA positive

[Schmidt et al., Vox. Sang. 2001, 81:228-235]
## Detection of B19 DNA in Plasmapools and SD Plasma (PEI results)

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<th>S/D-Plasma</th>
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<td><strong>anti-B19-IgG</strong></td>
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¹ n.d. = not determined

[Schmidt et al., Vox. Sang. 2001, 81:228-235]
Parvovirus B19 DNA in Blood Products (PEI results)

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**Antithrombin III:**
19% positive (<3log$_{10}$ geq/mL)

**Immunoglobulins and Albumin:**
8% positive (<4log$_{10}$ geq/mL)

[Schmidt et al., Vox. Sang. 2001, 81:228-235]
Permissive host cells for Parvovirus B19

Omnipotent haematopoetic stem cell

- BFU-E
- CFU-E

Erythroblast/
Pronormoblast

- Retikulocyt
- Erythrocyt

Ku812Ep6 Cells
(Miyagawa et al., 1999)
B19 - Infected Ku812Ep6 Cell

2 µm

250 nm

[Blümel, unpublished]
# Infectivity of Plasma-Samples

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<th>IgG</th>
<th>IgM</th>
<th>B19-DNA (log_{10} geq/mL)</th>
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*: in house standard

**Immunofluorescence**:

1 ifu = 4-5 \log_{10} \text{geq}

**RT-PCR**:

1 mRNA_{50} = 3-4 \log_{10} \text{geq}

Inactivation of Parvovirus B19 (B19) versus Porcine parvovirus (PPV) at Pasteurisation of 5% Albumin

Infectivity (log$_{10}$ ifu/mL or log$_{10}$ TCID$_{50}$/mL) vs Time (min)

Inactivation of Parvovirus B19 (B19) versus Porcine parvovirus (PPV) at Pasteurisation of 5% Albumin

Capsid Structure of Paroviruses

Canine Parvovirus

Parvovirus B19

[Chipman et al., 1996, PNAS 93:7502-7506]
B19-Infection in German Hemophiliacs

Analysis of two Transmission Cases

Two children with haemophilia A at high dose therapy

DNA sequence analysis from patients, products, and environmental B19V samples showed transmission by clotting factors

Patient A received 180 mL containing $8.6 \times 10^6$ geq/mL; Sum: $1.6 \times 10^9$ geq
Patient B received 230 mL containing $4.3 \times 10^4$ geq/mL; Sum: $9.9 \times 10^6$ geq

- Products had been manufactured from highly-viraemic plasma-pools ($10^8$ genomes per mL in case B)
- The applied heat treatment (dry heat or steam heat) did not completely the inactivate the high or medium load B19V

## Genomic B19V Fingerprints

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Genetic Relation of B19V samples
(relative genetic distance calculated with maximum likelihood algorithm)

Manufacture of Product B (FVIII) from highly-contaminated Plasma Pools

Pool 1 $10^7$ geq/mL
Pool 2 $10^6$ geq/mL
Pool 3 $10^6$ geq/mL
Pool 4 $10^5$ geq/mL
Pool 5 $10^2$ geq/mL
Pool 6 $10^2$ geq/mL
Pool 7 $10^2$ geq/mL
Pool 8 $<10^2$ geq/mL

Product B $4 \times 10^4$ geq/mL

B19 transmission from high purity FVIII

Investigated a case report received by the FDA for the possible transmission by a high-purity factor VIII concentrate

Causal relationship between the product and the recipient

Infection occurred when the seronegative recipient received 30,000 geq of B19 DNA

Product manufactured from a highly viraemic plasma pool

[Mei-ying W Yu (FDA), unpublished data]
B19V Transmissions by SD Plasma
(post marketing study, Vitex)

SD-plasma containing **high titers** of B19V ($10^6$ to $10^{8.5}$ genomes per mL)

7 from 19 recipients seroconverted after 7 days
18 from 19 recipients seroconverted after 3 months
14 from 18 recipients showed viremia after 3 months

SD-plasma containing **low titers** of B19V ($10^{0.5}$ to $10^{3.5}$ genomes per mL)

0 from 58 recipients seroconverted
0 from 58 recipients showed viremia after 3 months

## Symptomatic B19V Infections and implied Plasma-Products

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<th>virus inactivation</th>
<th>Patients (age)</th>
<th>Underlying Disease</th>
<th>Symptoms</th>
<th>Reference</th>
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<td>male (1a)</td>
<td>haemophilia B</td>
<td>exanthema, arthralgia, 35d post infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>male (20a)</td>
<td>haemophilia B</td>
<td>exanthema, fever, 12d post infusion</td>
<td></td>
</tr>
</tbody>
</table>
Summary

• Certain risk groups can be identified (immunosuppressed Patients, patients with haemorrhagic disorders, pregnant women)

• Clotting factors are at main risk for B19 transmission
  With ethanol-fractionated albumin, there is substantial removal and inactivation. With immunoglobulins, there is some removal/inactivation and indication of effective neutralisation.

• In the few transmission cases which have been investigated in detail, highly-contaminated plasma pools were involved.
Present Safety Measures against B19V

Recommendation to use blood from IgG positive donors for transfusion of patients at risk.
Information of doctors to draw attention on possible B19V-infections
National body in Germany (‘Arbeitskreis Blut’)

Introduction of an effective non-enveloped virus inactivation/removal step
For plasma-derived medicinal products [Guideline CPMP/BWP/269/95]
Complete inactivation/removal is, at present, difficult to realize for several clotting factors considering the high loads in plasma.

Ph. Eur. on Human Plasma pooled and treated for virus inactivation
Limit: less than $10^4$ IU B19V DNA per mL
See transmission cases by SD-Plasma

Ph. Eur. on Human anti D Immunoglobulin
Limit: less than $10^4$ IU B19V DNA per mL
Precautionary measure for an identified risk group

Screening of all plasma for fractionation
Limit of less than $10^5$ IU B19V DNA per mL (PPTA voluntary standard)
Limit of less than $10^4$ IU B19V DNA per mL (LFB standard)
This measure includes clotting factors
Points for Discussion:

1. Is a high titer limit of all plasma pools desirable/reasonable?

2. Is a voluntary measure sufficient/desirable?

3. What should be the limit: $10^4$ versus $10^5$?
Draft Chapter on Viral Risk Assessment
(Chapter 6, Guideline CPMP/BWP/269/95)

“The aim of this chapter is to outline the general principles that manufacturers should follow in performing a risk assessment with respect to potential virus-transmission from plasma-derived medicinal products and the basis for its evaluation by the competent authorities.”
General Principles

- Determine frequency and potential level of virus contamination in the plasma pool "potential virus input".
- Weigh up "potential virus input" against "overall virus inactivation/removal capacity".
- Estimate risk for a final dose (vial) (No definition of a "safety limit" for the final product).
<table>
<thead>
<tr>
<th>Purification step</th>
<th>Titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
</tr>
</tbody>
</table>

Virus Validation
Points for Discussion

• Definition of a safety limit for a final product?

• Ratio of particles to infectivity?
  Is there a reliable data base? Can results from animals/cell culture be extrapolated?

• Impact of antibodies in pool/product intermediates/final product
  is there any neutralization in the plasma pool?
  is there dissociation of virus/antigen complexes during manufacture?
  removal of virus/antibody complexes?
  how to quantify neutralisation by antibodies in final product?

• Full range of inactivation/removal is difficult to determine for very effective steps
  Sum of log reduction factors from single steps

• How to consider qualitative aspect of virus validation experiments
  (e.g. adequacy of model virus, quality of down-scaling,)

• Contribution of clinical studies or clinical experience

• Is an accumulation of worst case assumptions realistic/valuable?

• Consider single treatment vs. life-long treatment
Parvovirus B19

In-process Control Testing of Source Plasma

Stephen R. Petteway, Jr., Ph.D.
Bayer Biological Products
for
The Plasma Protein Therapeutics Association
Parvovirus B19 Infection

- Parvovirus B19 infections typically resolve with the appearance of neutralizing antibodies ~10 days post infection for IgM and ~17 days post infection for IgG.
- Period of viremia ~14 days.*
- Intense viremia develops approximately one week after infection, and viremia usually lasts one week.

*In some cases it has been observed that individuals continue to produce low level Parvovirus B19 for a longer period of time.
Parvovirus B19 DNA Profile

Viral Load (IU/mL)

Day

Absorbance (P/N)

Elevated

Targeted Cut-off

Non-elevated

IgG (Erdman et al., 1991)

IgM (Erdman et al., 1991)

March 11, 2004

EID Round table
Parvovirus B19 Different Testing Paradigm

<table>
<thead>
<tr>
<th></th>
<th>HIV, HCV, HBV</th>
<th>B19</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td>Chronic</td>
<td>Acute</td>
</tr>
<tr>
<td><strong>Public Health</strong></td>
<td>+++++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Threat</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevalence</strong></td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Virus Titer</strong></td>
<td>$\leq 10^7$</td>
<td>$\leq 10^{13}$</td>
</tr>
<tr>
<td><strong>Process Reduction</strong></td>
<td>Effective</td>
<td>Marginal</td>
</tr>
<tr>
<td>Prior to NAT testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Margin of Safety</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Safety Approach</strong></td>
<td>Plasma screening Validate viral reduction</td>
<td>In-process control Validate viral reduction</td>
</tr>
</tbody>
</table>
History

• 1998-1999 Industry begins to assess impact of various strategies on detection and removal of Parvovirus B19-reactive units - opts to pursue differential identification and removal of high-titer units

• Q4 1999 FDA proposes strategy for limiting viral loads in plasma manufacturing pools based on information gathered during the investigation of seroconversions associated with S/D plasma

• Q3 2000 EMEA Workshop on Virus Safety of Plasma-Derived Medicinal Products with Particular Focus on Non-Enveloped Viruses

• Q4 2000 Release of the WHO International Standard for Parvovirus B19 DNA (99/800) at $5 \times 10^5$ IU/vial

• Q2 2001 Plasma Protein Therapeutics Association (PPTA) issues voluntary standard for manufacturers
### Objectives

- Reduce further the potential risk of Parvovirus B19 transmission
- Maintain protective antibody titers that contribute to efficacy of Ig products
- Allow independent strategies for screening and load reduction
- Limit viral loads in plasma manufacturing pools to levels below $10^5$ IU/mL
- Continue research on the inactivation and removal of non-enveloped viruses

### Time Frame

- Implement testing of incoming plasma no later than end of 2001
- Manufacturing pool titers below $10^5$ IU Parvovirus B19 DNA/ml no later than July 01, 2002
Pathogen Safety is a comprehensive approach with effective redundant measures that provide a high margin of safety.
Parvovirus B19 Management is part of the comprehensive approach with effective redundant measures that provide a high margin of safety

Donor

Plasma Donation Center

Safety Step 1: Donor Screening

Safety Step 2: Testing Donation

Safety Step 3: Inventory Hold and Lookback

Begin Manufacturing

Safety Step 4: Plasma Pool In-process control

Safety Step 5: Virus Inactivation Virus Removal

Complete Manufacturing

Safety Step 6 & 7: Quality Assurance GMP

Safety Step 8: GCP Packaging Guidance

Safety Step 9: Post-Marketing Surveillance

March 11, 2004

EID Round table
Reduction in Parvovirus B19 Viral Loads

Pre-implementation

No Testing

10^1 - 10^9 IU/mL

Viral Reduction

Production Pool

Margin of Safety

Post-implementation

High Titer Units

Minipool Testing

96-1200 samples

<10^5 IU/mL

Viral Reduction

Increased Margin of Safety

Production Pool
Manufacturing processes differ throughout the industry.

Each manufacturer has set the testing threshold based on the size of minipools and manufacturing pools to achieve the PPTA voluntary standards.
NAT Sensitivities for Minipool Testing and Original Donations

Minipool testing - targeted testing threshold

<table>
<thead>
<tr>
<th>Company</th>
<th>Sensitivity (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>$1.5 \times 10^4$</td>
</tr>
<tr>
<td>Company B</td>
<td>$2.3 \times 10^4$</td>
</tr>
<tr>
<td>Company C</td>
<td>$3.7 \times 10^3$</td>
</tr>
<tr>
<td>Company D</td>
<td>$5.0 \times 10^3$</td>
</tr>
</tbody>
</table>

- The sensitivities required to achieve reduced manufacturing pool loads are a function of the minipool size and the manufacturing pool size.
- Minipool and manufacturing pool sizes vary across the industry.
- Each manufacturer has set the testing threshold based on the size of minipools and manufacturing pools to achieve the PPTA voluntary standards.
NAT sensitivities for minipool testing and original units

Minipools that are reactive based on the targeted threshold are assessed and units are released or discarded based on individual company process to achieve the PPTA voluntary standard.
Effect of Current Strategy

- The elimination of high titer Parvovirus B19 units results in a consistent reduction in plasma manufacturing pool viral loads.
- A $1 \log_{10}$ margin reduces the exposure for unnecessary loss of plasma.
B19 DNA in Manufacturing Pools

Prior to B19 in-process NAT

After B19 in-process NAT Implementation

The data clearly demonstrate the value of the in-process control testing by B19 NAT
Clinical Performance
July 2000-December 2003

- Total individual donations: $9.3 \times 10^6$
- Total mini-pools: 96,875
- Total reactive donations: 4,303
- Hit rate: 1:2,161
- Analytical sensitivity: $1.7 \times 10^3$ IU/mL
  (validated at $5 \times 10^3$ IU/mL)
Clinical Performance
July 2000-December 2003

Trends in the incidence of parvovirus B19 infections

- Collection date
- Test date

Incidence (donations/100,000) vs. Month
In process control measures are designed to enhance the safety margin of plasma therapies.

Parvovirus B19 NAT lacks value as a diagnostic or donor screening method.
Factors Influencing Resolution Time

• Shipping logistics
• Laboratory capacity and through-put
  • Pooling
  • Testing
  • Resolution
• Seasonality of infections
Resolution Time: Collection to Result
Does not include time for confirmation testing or notification of donor

<table>
<thead>
<tr>
<th>Company</th>
<th>Single Units: Mean and [Range], (Days)</th>
<th>Single Donor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>40</td>
<td>Not done</td>
</tr>
<tr>
<td>Company B</td>
<td>38 [8-79]</td>
<td>Not done</td>
</tr>
<tr>
<td>Company C</td>
<td>50-60</td>
<td>Not done</td>
</tr>
<tr>
<td>Company D</td>
<td>25 [9-57]</td>
<td>Not done</td>
</tr>
</tbody>
</table>
Donor Notification/Counseling

- Average resolution time for NAT testing ranges from 25-60 days.
- Additional time would be required to identify the unit, perform confirmatory testing, and communicate with the donor.
- Infected donor would have already cleared the virus and developed sufficient antibodies to confer a life-long immunity by the time notification occurred.
- The infected donor would have already passed the infection to close contacts by the time of notification.
Anti-Parvovirus B19 Antibody Content in Manufacturing Pools

- Anti-B19 antibody level is not affected by implemented in-process control measures
- 98% of manufacturing pools above 10 IU per mL
- No manufacturing pools below 5 IU per mL

Demonstrates appropriate strategy for effective management of Parvovirus B19 loads in manufacturing pools while retaining necessary antibody levels
PPTA member companies have implemented appropriate processes which have been shown to be effective in managing Parvovirus B19 in manufacturing pools thus achieving an increased margin of safety for life-saving plasma protein therapies
Backups
BPAC: Parvovirus B19

• September 1999 BPAC
  – Recommendation to treat Parvovirus B19 testing as in-process control
  – No studies required to validate clinical efficacy of B19 NAT under IND for plasma for further manufacture
  – Validation as an analytical test only
  – No clinical correlates if no decisions regarding donor or recipient management are taken
Collection-to-Result Lag Involved in Parvovirus B19 Testing

IgG (Erdman et al., 1991)  
IgM (Erdman et al., 1991)

Quartile 1 2 3 4

Viral Load (IU/mL)

Absorbance (P/N)

Targeted Cut-off

Collection-to-result lag (n=1099)
Factors Affecting Effectiveness of Donor Notification

- Interdiction period is limited
  - mean = 28 days (s.d. = 17 days)
  - median = 22 days
- Number of elevated donations interdicted is dependent on donation frequency (n = 68 donors)
  - average number interdicted is 5 donations
  - range = 1-8 donations
- Benefits of notification are unclear
  - Chance of detecting pre-peak donation: 20% (1 in 5)
  - Chance that notification could occur within median time-frame: 50%
  - Opportunity to provide relevant information during period of elevated viremia: 10%
Impact of Threshold Requirements on Destruction of Plasma Pools

Threshold
(Plasma Manufacturing Pool)

<table>
<thead>
<tr>
<th>IH/mkL</th>
<th>10^7</th>
<th>10^6</th>
<th>10^5</th>
<th>10^4</th>
<th>10^3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Pool Volume (liters)</td>
<td>8,000</td>
<td>4,000</td>
<td>1,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure per manufacturer (pools/year)</td>
<td>1 to 5</td>
<td>MORE</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

March 11, 2004
EID Round table
Cross-contamination by high-titer Parvovirus B19 donations occurs today

- **Pre-NAT**: preparation of test samples (pilot tube)
- **Pooling**: master pool preparation
- **NAT**: reaction setup, post-NAT handling

As sensitivity in fractionation pool is increased, then sensitivity in the mini-pool has to increase accordingly resulting in a reduced possibility to discriminate true reactives from false reactives.
Detection of Parvovirus B19 reactive donations in a minipool [512]

- Reactive donations are interdicted by testing rows, columns, and layers
- 1 reactive donation is interdicted by performing 8+8+8 assays
- As test sensitivity increases number of tests required increases exponentially
FDA Issues to be Addressed

• Testing algorithm for identifying, retrieving and management of reactive (high-titer) units/donors
• NAT sensitivities for minipool testing and original units
• Prevalence of reactive:
  – Minipools
  – Original units
  – Manufacturing pools
  – Levels of B19 DNA in each
• Time to resolve to single units
• Time to resolve to single donors
• Prevalence and levels of anti-Parvovirus B19 antibodies, if any
• Profiles of B19 DNA, anti-B19 IgM and anti-B19 IgG in serial bleeds, if any
Prevalence of reactive

- Minipools
- Original units
- Manufacturing pools

Levels of B19 DNA in each
Parvovirus B19 Infection

- Acute, self-limiting disease without chronic sequelae in normal individuals.
- Normally transmitted via the respiratory route.
- Most infections are asymptomatic. Where symptomatic, (fever, headache, malaise, myalgias, rash) the donor would be deferred.
- Antibodies to Parvovirus B19 confer life-long protective immunity.
- More significant sequelae are rare and usually occur in particularly susceptible non-donor populations with pre-existing conditions.

Parvovirus B19 Infection

At Risk Populations and Close Contacts

• At risk populations are deferred
  ➢ Are you feeling well and healthy today?
  ➢ Female donors: In the past six weeks, have you been pregnant or are you pregnant now?
  ➢ Immuno-compromised individuals

• No potential for preventing transmission of infection to close contacts
  ➢ Mean Turn-around times (25 to 60 days)
  ➢ Confirmation testing (minimum of additional 10 days)
  ➢ Donor Notification (3 days to months)
Conclusions

• Medical information would be nonactionable for both the donor and his/her close contacts
• Questionable ethics in the notification of donors regarding nonactionable medical information
• Counseling a donor regarding nonactionable medical information presents difficulties
• Donor notification/counseling lacks public health benefit
  – Non-chronic, acute, short duration viral infection
  – Highly prevalent in general population
Prevalence and levels of anti-Parvovirus B19 antibodies, if any
NAT Sensitivities

Original units: Targeted threshold (calculated)

<table>
<thead>
<tr>
<th>Company</th>
<th>Threshold (IU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>$7.7 \times 10^6$</td>
</tr>
<tr>
<td>Company B</td>
<td>$1.2 \times 10^7$</td>
</tr>
<tr>
<td>Company C</td>
<td>$4.4 \times 10^6$</td>
</tr>
<tr>
<td>Company D</td>
<td>$5 \times 10^5$</td>
</tr>
</tbody>
</table>

Each manufacturer has set the testing threshold based on the size of minipools and manufacturing pools to achieve the PPTA voluntary standards.
## Prevalence and Levels of B19 DNA in Minipools

<table>
<thead>
<tr>
<th>Company</th>
<th>Frequency in Reactive Minipools</th>
<th>B19 DNA Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>1/25 minipools</td>
<td>Up to $10^9$ IU/ml</td>
</tr>
<tr>
<td>Company B</td>
<td>1/12 minipools</td>
<td>Not determined</td>
</tr>
<tr>
<td>Company C</td>
<td>1/3 minipools</td>
<td>$&gt;10^{3.7}$ IU/ml</td>
</tr>
<tr>
<td>Company D</td>
<td>1/40 minipools</td>
<td>Up to $10^{11}$ IU/ml</td>
</tr>
</tbody>
</table>

Frequency in minipools is influenced by the size of minipools
### Frequency & Levels of B19 DNA in Original Donations

<table>
<thead>
<tr>
<th></th>
<th>Frequency of Discarded Units</th>
<th>Calculated B19 DNA Level in Targeted Donations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company A</td>
<td>1 / 5,000</td>
<td>$\geq 7.7 \times 10^6$ IU/ml</td>
</tr>
<tr>
<td>Company B</td>
<td>1 / 3,710</td>
<td>$\geq 1.2 \times 10^5$ IU/ml</td>
</tr>
<tr>
<td>Company C</td>
<td>1 / 4,630</td>
<td>$\geq 4.4 \times 10^6$ IU/ml</td>
</tr>
<tr>
<td>Company D</td>
<td>1 / 2,100</td>
<td>$\geq 5.0 \times 10^5$ IU/ml</td>
</tr>
</tbody>
</table>
Case Study: vCJD in the UK

Bob Perry, Brian McClelland, Peter Foster: SNBTS

PPTA Emerging Infectious Diseases Roundtable
Brussels
March 11, 2004
Session 0810-0910
Outline

• The BSE story 1987-1996
• The players
• Blood 1996-9
• Situation report  March 2004
• The next 10 years?
• Lessons
The Phillips Report 2000


EAPPI vCJD March 2004
Remit of the BSE Enquiry

To establish and review the history of the emergence and identification of BSE and variant CJD in the United Kingdom, and of the action taken in response to it up to 20 March 1996; to reach conclusions on the adequacy of that response, taking into account the state of knowledge at the time; and to report on these matters to the Minister of Agriculture, Fisheries and Food, the Secretary of State for Health and the Secretaries of State for Scotland, Wales and Northern Ireland.
BSE has caused a harrowing fatal disease for humans.

As we sign this Report the number of people dead and thought to be dying stands at over 80, most of them young. They and their families have suffered terribly.

Families all over the UK have been left wondering whether the same fate awaits them.
A vital industry has been dealt a body blow, inflicting misery on tens of thousands for whom livestock farming is their way of life.

They have seen over 170,000 of their animals dying or having to be destroyed.

BSE developed into an epidemic as a consequence of an intensive farming practice - the recycling of animal protein in ruminant feed. This practice, unchallenged over decades, proved a recipe for disaster.
In the years up to March 1996 most of those responsible for responding to the challenge posed by BSE emerge with credit.

At the heart of the BSE story lie questions of how to handle hazard - a known hazard to cattle and an unknown hazard to humans.

The Government took measures to address both hazards. They were sensible measures, but they were not always timely nor adequately implemented and enforced.
The rigour with which policy measures were implemented for the protection of human health was affected by the belief of many prior to early 1996 that BSE was not a potential threat to human life.

The Government was anxious to act in the best interests of human and animal health. To this end it sought and followed the advice of independent scientific experts - sometimes when decisions could have been reached more swiftly and satisfactorily within government.
The Government introduced measures against the risk that BSE might be a matter of life and death ... for humans but this risk was not communicated to the public ...

The Government did not lie to the public about BSE.

It believed that the risks posed by BSE to humans were remote. It was preoccupied with preventing an alarmist over-reaction to BSE because it believed that the risk was remote.

This campaign of reassurance was a mistake. When on 20 March 1996 the Government announced that BSE had probably been transmitted to humans, the public felt that they had been betrayed.

Confidence in government pronouncements about risk was a further casualty of BSE.
Individual cattle were probably first infected by BSE in the 1970s. If some lived long enough to develop signs of disease, these were not reported to or subject to investigation.

A cow had succumbed to BSE in September 1985, but the nature of the disease that had caused its death was masked by other factors and was not recognised.

Two further cases of BSE at the end of 1986 were identified as likely to be due to a Transmissible Spongiform Encephalopathy (TSE) in cattle.
Knowledge about BSE was not concealed from the public. However, the public was not informed of any change in the perceived likelihood that BSE might be transmissible to humans and was repeatedly reassured that it was safe to eat beef.

Some public statements conveyed the message not merely that beef was safe but that BSE was not transmissible.

The impression thus given to the public that BSE was not transmissible to humans was a significant factor leading to the public feeling of betrayal when it was announced on 20 March 1996 that BSE was likely to have been transmitted to people.
On learning of BSE in March 1988 the CMO, Sir Donald Acheson, sought to ensure that the potential risks that the disease posed in relation to human medicinal products were addressed. However, Medicines Division (MD) did not bring the matter before their advisory committees until November 1988. Of this period, two months' delay was attributable to a failure to accord the matter appropriate priority.
• Human vaccines prepared using bovine tissues may have been used up to 1992

• Decision to continue using existing stocks of vaccines was not considered to need Ministerial approval. We consider that Ministers would have accepted the overwhelming professional advice, but would have insisted that the process of phasing out these stocks was more vigorously pursued.

• Officials in the MCA and VMD not systematically accountable to anyone for the manner in which the phasing out exercise was handled. Nor, given the low-profile handling, was there any parliamentary or public scrutiny of their actions.
The conclusion was reached by SEAC on 16 March 1996 that the most likely explanation for the cases of a new variant of CJD in young people was exposure to BSE.

It should have been apparent to both MAFF and DH by early February 1996 that there was a serious possibility that ... BSE had been transmitted to humans.

The two Departments should have worked together with SEAC, to explore the possible policy options.

There was no interdepartmental consideration of policy options until March 1996. The views of SEAC were awaited whether the cases of vCJD were linked with BSE, and on what action should be taken. This was an inadequate response.
The players...

- CVL (Central Veterinary Laboratory)
- SEAC
- MSBT
- Departments of Health (England, Scotland, Wales, N Ireland)
- MAFF
- Medicines Division
- CPMP
- NBS, SNBTS, NIBTS, WBTS
- JPAC
- SACTTI
- vCJD Surveillance unit
- MRC
Blood 1995-6

1995  May: MoH Scotland (CRAG) publishes report Optimal Use of Donor Blood

1996  March: UK MoH announces new form CJD in humans: Probably related to BSE

1996  April: UK Blood Services (SACTTI subcommittee of JPA meet CJDSU. Notification procedures agreed for patients with vCJD who had donated blood C)
Jan  PrPSc detected in tonsil of vCJD patients

March: WHO reviews blood component risks. P Brown’s data suggests components should be infectious

Oct  Bruce et al (Nature) BSE and vCJD probably the same agent. SEAC advises leucodepletion of blood for transfusion. Based on Aguzzi paper claiming B-Cells needed for infection (Nature) Now disproven

Oct and Nov. Recalls of Albumin and FVIII by BPL (donor to pool developed vCJD) Affect 46 Countries. Includes Pulmonate imaging product

Dec  Risk assessment by DNV commissioned by DOH
    UK Haemophilia directors recommend suspension of use of UK plasma derived F VIII

EAPPI vCJD March 2004  17
Blood 1998-9

1998

Feb    CPMP advises plasma derivatives be withdrawn if contain a vCJD associated. Albumin from countries with cases of vCJD not to be used as excipient

Feb    UK DoH authorise importation of plasma for fractionation

May    DOH confirms UK plasma not to be used for fractionation

July   DoH announces all blood components to be leucodepleted

1999

Feb    DNV Risk assessment concludes best risk reduction options are elimination of UK plasma from fractionated products and leucodepletion of all blood components
Blood 1999-2004

- **2000 May**  SNBTS Effective Use of Blood project initiated
- **2001 Oct**  CJD Incidents panel: Consultation paper on management of exposure by medical procedures (transfusion, surgical instruments)
- **2003 April**  NHS Scotland Better Blood Transfusion programme commenced
- **Aug**  DOH announces FFP to be imported for all born after 1 Jan 1996
- **2004**  Still evaluating exclusion of previously transfused donors
- Extension of FFP Importation
- Preparations for evaluation, implementation of screening tests
- Total cases **150**
The next 10 years

Escalating costs - filtration, plasma importation

Falling supply - 5% or more if exclude transfused donors

Worried donors and patients - increased perception of general population being at risk

Pressure for blood conservation technologies
The next 10 years

Pressure to deploy first available screening test

Likely to have huge false positive rate

Donor information and counselling problematic

Likely to further discourage donors
The next 10 years

All cases current forecast 5-600
Transfusion cases ??? Maybe 10???
Uncertainty “second wave” cases

*Will benefits of precautionary approach outweigh risks of:*

- Shortages
- Public concerns
- Escalating costs
- New risks due to changes in clinical practice
- An enforced reversal of an element of the precautionary policy
Lessons....?

Inadequate management of BSE left incoming Government feeling highly vulnerable
Precautionary approach was an inevitable consequence
On the assessment of human risks and impact of precautionary actions, Government drove, science followed.
Political necessity removed consideration of benefit for cost
Scientists benefited from “open chequebook “funding
Animal experiments started very late
Only TSE research centre in UK closed just before the BSE epidemic “research of insufficient practical value”.

EAPPI vCJD March 2004
If we were to do it all again...

Start animal experimental programme much earlier
Invest more to ensure excellent data on patterns of blood use and traceability
Invest proportionately more in comprehensive blood management programme- to reduce population at risk of needing transfusion
More investment in public education about nature and unavoidability of very small risks, in context of all medical risks
BUT, given a climate similar to that of 1996-9 in UK, many of the actions likely to be similar.
Severe Acute Respiratory Syndrome (SARS)
Global Alert, Global Response

World Health Organization
Sever Acute Respiratory Syndrome: SARS

- Atypical pneumonia
  - rapid clinical course of disease; severe outcome
- Affected mainly health care workers caring for cases and their contacts
- Index cases had history of travel to South China
- International spread
SARS OUTBREAK, 2003
International spread

Infectious diseases will continue to emerge...

Some 30 new diseases have cropped up since mid-1970s – causing millions of deaths
SARS Transmission

Index case
(first generation)

Second generation =
close and direct contact with health care workers (HCW) or others

Third generation =
family members of HCW

Fourth generation =
other contacts in community

- close and direct contact
- environmental factor, Hong Kong
SARS Response: “Building the Ship while Sailing”

- New disease, lots of unknown
- UNCERTAINTY

Information & Evidence
the key in defining the response
SARS: Global Alert

- **12 March**
  
  First global alert describing atypical pneumonia in Viet Nam and Hong Kong

- **15 March**
  - **Singapore**: medical doctor with atypical pneumonia fitting description of 12 March reported by Ministry of Health on return flight from New York

  Second, more precise and urgent global alert to international travellers
  
  - Case definition provided
  - Name (SARS) announced
  - Advice given to international travellers to raise awareness
Global Alert, 15 March 2003
using the public health evidence

1) Atypical pneumonia with rapid progression to respiratory failure

2) Health workers appeared to be at greatest risk

3) Unidentified cause, presumed to be an infectious agent

4) Antibiotics and antivirals did not appear effective

5) Spreading internationally within Asia and to Europe and North America
PROBABLE CASE: *current definition*

1. A suspect case with radiographic evidence of infiltrates consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray
2. A suspect case of SARS that is positive for SARS coronavirus by one or more assays
3. A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause
SUSPECT CASE: current definition

1. A person presenting after 1 November 2002 with history of:
   - high fever (> 38 °C)
   - cough or breathing difficulty
   - one or more of the following exposures during the 10 days prior to onset of symptoms:
     • close contact with a person who is a suspect or probable case of SARS
     • history of travel to or residing in an area with recent local transmission of SARS

2. A person with an unexplained acute respiratory illness resulting in death after 1 November 2002, but on whom no autopsy has been performed
   - one or more of the following exposures during to 10 days prior to onset of symptoms:
     • close contact with a person who is a suspect or probable case of SARS
     • history of travel to or residing in an area with recent local transmission of SARS
SARS: cumulative number of probable cases worldwide as of 28 May 2003 – Total: 8,240 cases, 745 deaths

- China (5,323)
- Hong Kong (1,728)
- Taiwan (610)
- Singapore (206)
- Malaysia (5)
- Canada (149)
- US (66)
- US (66)
- Colombia (1)
- Brazil (2)
- South Africa (1)
- Mongolia (9)
- Kuwait (1)
- India (3)
- Korea Rep (1)
- Japan (1)
- Macao (1)
- Thailand (1)
- Australia (6)
- New Zealand (1)
- Philippines (1)
- Indonesia (2)
- Malaysia (5)
- South Africa (1)
- Kuwait (1)
- India (3)
- Mongolia (9)
- Colombia (1)
- Brazil (2)
- Canada (149)
- US (66)

**Outbreaks before 15 March global alert**

**Outbreaks after 15 March global alert**
WHO Global Role, Regional and country work

Objectives:
- Control outbreak
- Identify causative agent
- Identify effective interventions
- Provide support to countries
- Public and professional information
- Limit impact on travel and trade
Evidence Building, Information Sharing

Coordination and facilitation by WHO

- Teams of international experts sent to the field to verify data and advise Govt on preparedness and response to outbreak

- Global Networks established (Laboratory, Epidemiology, Clinical, Environment, Blood Safety, Animal Reservoir)

- Epidemiological investigations and support for research
  - Official notification, Rumour surveillance, Cross-border investigation involving multiple countries

- Guidelines developed based on available evidence and best practice

- Mechanisms developed for international coordination and teleconferencing
Global Outbreak Alert Network

- Global Outbreak Alert & Response Network: a technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance.

- The Network provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond.

WHO Preparedness Guidelines

- Country Preparedness Check List
- National Preparedness Guidelines
- Assessment Protocol for National Preparedness

http://www.wpro.who.int/sars/
WHO Infection Control Guidelines and Tools

- Infection Control Guidelines
- Presentations for training
- Training Video
- Key documents on CD
- Press releases
- Q&A fact sheets
- Websites
SARS and the media
Media

Overwhelming attention: Media can be your best friend or your worst enemy

Credibility of the Organization

• Media informing WHO (rumours, research, reports)
• Media informing the public – Govt (raise awareness, …)
• WHO informing the Media
  – Daily press releases, Press conference, Interviews journals, radio, and TV
• What, who …
  – develop clear messages
  – Be clear about what you know and what you don’t know
  – Make statements on matters you have assessed yourself; don’t assume
SARS Outbreak

Implications for Blood Safety
Emerging Diseases - Issues for Blood Safety

- **Is the disease transmissible via transfusion?**
  - Until evidence is obtained proving or disproving transmission, all measures are *precautionary*.

- **What means are available to prevent (even if theoretical) transmission?**
  - Donor issues - *This is of major importance*
  - Laboratory issues
  - Appropriate clinical use of blood
The Safety Tripod in Blood Transfusion

Donor selection → Testing → Elimination/removal

How strong are these measures in respect to SARS?
Issues in Blood Safety and SARS

- **Impact of SARS on blood safety** (labile blood components and plasma derivatives)
  - potential of transmission unknown
  - possibility of viraemic period, before/after SARS
  - precautionary deferral of blood donors
  - post donation information
  - transmission through plasma derivatives unlikely

- **Impact of SARS on blood availability**
  - Decrease in donations due to donor deferrals
  - Donors’ apprehension in blood donation
Safety through Donor Selection

- Deferral measures in place - WHO recommendations; individual agencies
- Alignment to travel advisories - flexibility
- Uncertainty on post-exposure deferral period
- Uncertainty on length of deferral post recovery
SARS transmission pattern

- No evidence of transmission before onset of first symptoms

- A few cases thought to have transmitted in the early prodromal period (small # of source cases, Canada)

- Those who are very ill or experiencing rapid clinical deterioration, usually during second week of illness, are the most communicable

- No evidence of transmission 10 days post-fever resolution
Patterns of viral shedding in clinical cases

Possible pre-symptomatic viraemia?
**Virus stability**

- **Virus survives**
  - stool and urine for at least 2 days
  - diarrhoeal stool up to 4 days
  - dried at room temperature at least 2 days
  - Acetone fixed slides
  - At -4 °C and -80 °C at least 21 days with minimal reduction

- **Does Not survive**
  - Usually used disinfectant
  - Temp 56 °C for 30 min in blood serum
  - fixed in infected cells after -20 °C Acetone fixation

Virus behaviour during fractionation?
Seroconversion
Clinical cases

Cumulative proportion of patients with seroconversion (%)

Time after onset of symptoms (days)

Peiris et al. Lancet: on line
Blood Safety Network

- Informal collaboration between interested parties to:
  - Review new information
  - Recommend / suggest action for blood services

  e.g. SARS - informal consultations led to recommendations on donor deferral periods as a precautionary measure

http://www.who.int/csr/sars/guidelines/bloodsafety/en/
WHO Recommendations on SARS and Blood Safety

15 May 2003

These guidelines are constantly reviewed and updated, as new information becomes available. They provide a generic basis on which national health authorities may wish to develop guidelines applicable to particular circumstances.

Although no probable SARS case has been ascribed to transmission by labile blood products or blood derivatives, and the mechanism of transmission of the SARS virus through transfusion of labile blood products*, since low viraemia has been documented 10 days after the onset of symptoms from probable SARS patients (see Identification of a Novel Coronavirus, Respiratory Syndrome).

The Department of Blood Safety and Clinical Technology (WHO/BCT), World Health Organization, proposes the following as precautionary principles to address the theoretical SARS risk through transfusion of labile blood products.
Lessons learnt (1)

- **Vulnerability of blood supply**
  - Potential transmission by blood
  - Effect on donor attendance
- **Need to strengthen donor programme**
  - Broaden donor base
  - Manage donor perceptions/fears
  - Use of media/communication tools
  - Requirement of staff and training
- **Impact of development of diagnostic test**
  - Application in blood screening depends on knowledge of viraemic state, methodology, infrastructure
Lessons learnt (2)

- Need to establish systems for traceability in blood transfusion services
  - Look back and trace back studies
- Develop contingency plans to address operational issues
  - Blood collection sites to be sited outside hospitals
  - Measures in case blood centre staff are infected
SARS - Areas of Uncertainty
Blood Safety Implications

- Presence and level of pre-symptomatic viraemia?
- Infectious phase post-recovery (viral shedding?)
- Stability of virus ex vivo?
- Viral marker patterns during viral replication - seroconversion
SARS: what did we learn

- In the world today an infectious disease in one country is a threat to all: **SARS does not respect national borders**

- Information provided early helped to contain the international spread of SARS

- SARS outbreak was contained by case detection, isolation and protection
SARS: what we did we learn

- Information and travel guidance can contain the international spread of an infectious disease
- Experts in laboratory, epidemiology and patient care can work together for the public health
- Infectious disease outbreaks reveal weaknesses in public health infrastructure
- Emerging infections can be contained with high level government commitment and international collaboration if necessary
SARS: what next?

Addressing health system deficiencies
- Review and improve hospital infection control standards
- Reinvest in Public Health and Public Goods

Strengthening and integrate SARS in overall surveillance system

Risk communication
- Remove unnecessary fears and educate the public
- Remove disincentives for reporting
SARS and the economy: Hong Kong
SARS: real and perceived risk

In addition to human suffering and death, SARS had a negative economic impact on Tourism, Travel and Trade due in part to discrepancy between real and perceived risk.