



The European Agency for the Evaluation of Medicinal Products
Pre-authorisation Evaluation of Medicines for Human Use

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EMEA WORKSHOP ON THE PLASMA MASTER FILE

10-11 October 2001

REPORT

SUMMARY

An EMEA Expert Workshop was held on 10-11 October 2001 to provide a forum for competent authorities, inspection services and industry to discuss their experience and new initiatives relevant to the current revision of the guideline on the "Plasma Master File" (PMF). The Workshop was divided into a restricted session, where the experience of the OMCLs and inspectorates with plasma pool testing and inspections respectively was discussed, and an open session where industry and interested parties were involved.

A number of issues were identified and discussed relating to: testing for viral markers; changes in the European legal environment; inspection of sites for collection, testing and storage of blood and plasma; industry quality systems; epidemiology of blood-borne infections in the donor population; experience and proposals for the content of the PMF.

The outcome of these discussions will be taken into account in the revision of the PMF Note for Guidance. In addition, points requiring further action will be taken forward through the appropriate channels.

1. INTRODUCTION

For blood and plasma-derived medicinal products, information on collection and control of the starting material, human blood or plasma, has to be documented as part of the dossier for marketing authorisation. This information is provided by using the format defined by the Note for guidance "Contribution to part II of the structure of the dossier for applications for marketing authorisation-control of starting materials for the production of blood derivatives" (EC III/5272/94). This documentation, which is contained in the "Plasma Master File", applies to all the blood and plasma-derived medicinal products of one company. The Note for guidance EC III/5272/94 is currently under review in order to update the headings and format. The workshop was organised to provide a forum for competent authorities, inspection services and industry to present their experiences and new initiatives and discuss their significance for the review of the note for guidance. The contribution of new initiatives to the further improvement of safety margins for blood products was discussed. Since testing by nucleic acid amplification technology (NAT) for viral nucleic acid had already been discussed at the September 2000 EMEA Workshop¹, discussions in this workshop were limited to the impact of NAT on other measures.

The workshop was divided into a restricted session for competent authorities and inspection services and an open session with industry. The restricted and open sessions on common subjects have been integrated in this report.

¹ Report of EMEA Workshop on Viral safety of plasma-derived medicinal products with particular focus on non-enveloped viruses, CPMP/BWP/BPWG/4080/00, 28 March 2001 and Addendum: Conclusions and recommendations of the BWP and BPWG, CPMP/BWP/BPWG/93/01, 28 March 2001 (<http://www.emea.eu.int/pdfs/human/bwp/408000en.pdf>)

2. TESTING FOR VIRAL MARKERS IN PLASMA POOLS (anti-HIV 1/2, anti-HCV, HBsAg and HCV RNA)

2.1 Experience of European competent authorities

Plasma pool testing for viral markers is mandatory for manufacturers of blood products for hepatitis B surface antigen (HBsAg), antibodies to HIV 1/2 and hepatitis C virus (HCV), and HCV RNA by nucleic acid amplification technology (NAT). As part of the Official Medicines' Control Laboratory (OMCL) batch release, these markers are also tested on samples of plasma pools by OMCLs. Since plasma pool testing has now been performed for many years, the findings and experience of the OMCLs was discussed in the restricted session.

As a general introduction, J-M. Spieser presented the OMCL testing and quality system. The European Department for the Quality of Medicines (EDQM) has a central role, as illustrated by the approach used to implement HCV NAT testing. The monograph making NAT testing for HCV RNA mandatory and the general method for testing were adopted by the Pharmacopoeia Commission, a European Working Standard has been established, and a set of validation plasmas is available. He presented the results of Proficiency Test Studies (PTS) which have been regularly organised with OMCLs since 1999. These PTS offer the OMCL control of their own testing competence and contribute to the consolidation of mutual confidence. Total success was seen in the last PTS (100% detection and no failures).

As part of the discussion, establishment of a parallel PTS system for manufacturers of blood products was suggested with regular reporting of performance in the annual update of the PMF.

R. Seitz gave an overview on the purpose and characteristics of plasma pool testing. The size of the pool and the design of the mini-pool testing strategy are decided by the manufacturers. He raised the question of whether a requirement for mini-pool testing is desirable. He proposed that the PMF should include:

- A clear definition of the plasma pool (e.g. maximal pool size and its range, whether the pool is the same for all products, the time point in manufacture where the first homogenous pool is generated, and the sampling strategy)
- Details of the mini-pool strategy
- Laboratories involved in testing, the test systems used and their validation for pool testing.

He emphasised that test kits are not designed for pool testing and that specific validation is required. He presented a comparison of diagnostic and dilution sensitivity of various test kits and emphasised that test kits with a high "dilution sensitivity" are needed for testing large pools. Test with a high "diagnostic sensitivity" may not necessarily have a high "dilution sensitivity". With the current knowledge that most manufacturers use mini-pool strategies, he considered that the place of plasma pool testing should be revised, since it could probably only be considered as a control to detect crude GMP deficiency (e.g. failure to discard positive donation(s)). On the basis of the experience gained, the discontinuation of pool testing for HCV-antibodies can be discussed since no positive pools have been detected, dilution sensitivity is poor, and HCV NAT testing is in place. Pool testing for HIV antibodies and HBsAg should be maintained since dilution sensitivity is much better and positive pools may be detected that would not be detected by NAT testing, if it were in place.

M. Ferguson reported on the experience of NIBSC and the approach used to validate each test, the relevant validity criteria and results. She confirmed that specific and careful validation of test kits is important.

G. Beck reported on the experience of the Austrian OMCL with plasma pool testing. He showed a decrease in measurable HBsAg due to complexation of low titre HBsAg with antibodies in a plasma pool. For HIV 1/2, screening tests with dilution sensitivity up to 1:300,000 are available and should be used. He proposed the development of a guideline for the validation of serological methods for plasma pool testing for use by OMCLs and manufacturers.

M. Wirz reported on the experience of the Italian OMCL. Recovery and linearity for material tested with a spike of anti-HIV and anti-HCV was sufficient whereas recovery for HBsAg spiked material was about 50%, which may be due to the presence of antibodies to HBsAg.

Considering the size of plasma pools, the chances of detecting a positive donation would be:

- Anti-HIV: 85% in the case of donations with a titre of approximately 1:10,000
- Anti-HCV: none: the detection limit is well below the mean size of the plasma pools
- HBsAg: 100% in the case of donations with a high titre (1:250,000) and 59% in the case of donations with a low titre (1:10,000).

She considered that it would be appropriate to test plasma pools for parvovirus B19 DNA.

2.2 Industry experience

The Industry described its experience with plasma pool testing during the open session.

A. Gröner described the PPTA experience with and strategy for plasma pool testing. PPTA member companies have implemented a voluntary standard to perform NAT testing for HBV DNA and HIV-1 RNA in addition to the mandatory testing for HCV RNA. NAT testing for parvovirus B19 DNA would be implemented from 2002.

During the discussion he commented that manufacturers have introduced mini-pool testing strategies as a tool to avoid the loss of large manufacturing pools due to a NAT positive result. Thus, it should be up to the manufacturers to decide on their pool-testing strategy and this should not be the subject of regulation.

B. Flan reported that small pool NAT testing for HCV RNA is already done routinely in a number of EU countries for the release of both cellular components and plasma. In addition some are introducing NAT testing for HIV RNA. He reported on the experience of LFB with mini-pool testing for HCV RNA since July 1997 and the incidence of seroconverting donations. One immunosilent carrier had been detected. He considered that NAT testing for parvovirus B19 contributes to increase the safety margin of plasma-derived medicinal products. He emphasised the importance of working in a GMP environment.

The following questions were addressed in both the restricted and open sessions:

- *What experience of testing is available (which labs are involved, which tests/markers, how many pools tested, negative/positive)?*

The OMCLs that presented their results (Austria, Germany, Italy, United Kingdom) reported similar results. Several thousands of plasma pools have been tested since the mid nineties for anti-HIV 1/2, anti-HCV, and HBsAg with one pool found positive for anti-HIV (HIV RNA not detected) and two pools above background for anti-HCV (also HCV RNA positive). One further pool was found HCV RNA NAT positive since testing became a requirement in 1999.

- *What should the future approach be in the light of the minipool strategy used by industry for NAT? Is there value in continuing with testing pools for HBsAg, and antibodies to HIV and HCV when NAT testing for HBV DNA, HIV and HCV RNA are done? If such testing is continued, should manufacturers test mini-pools in order to increase sensitivity?*

The OMCLs that presented their data agreed that the requirement for anti-HCV pool testing should be reconsidered. The available tests have poor dilution sensitivity and the more sensitive HCV NAT testing is now in place. In contrast, the dilution sensitivity of some HIV tests was good and a pool had been detected that was HIV antibody positive whereas HIV RNA was not detectable. The need for pool testing for HBsAg could be reconsidered in the future if NAT testing is generally introduced.

PPTA proposed that anti-HCV pool testing could be discontinued since it provides no gain in safety now that HCV RNA testing is performed. Before NAT testing for HCV RNA was introduced, the majority of HCV RNA NAT-reactive pools were antibody-negative. The possible replacement of pool tests for HBsAg and anti-HIV with NAT testing should also be assessed.

EPFA commented that serological and NAT testing of manufacturing pools for HCV, HIV and HBV represents a quality control of the source material for the manufacturer (and health authorities) for the release of batches of plasma. It is of limited value in increasing the safety

margin of plasma-derived medicinal products in a GMP environment with the implementation of NAT for the release of blood components.

Both EPFA and PPTA considered that there was no need to test for HBsAg and antibodies to HIV and HCV on mini-pools since testing is done at the individual donation level. B. Flan reported LFB's experience of testing mini-pools for HBsAg and antibodies to HIV 1/2 and HCV since 1996. No confirmed reactivity had been found and the practice of testing would be discontinued as it provided no added value.

- *If a manufacturer has tested mini-pools, is it necessary for the manufacturer to also test the manufacturing pool?*

Since most manufacturers are testing mini-pools by NAT, NAT testing of the plasma pool is only likely to detect a GMP deficiency (e.g. failure to discard positive donation(s)). Nevertheless, the only mandatory requirement is for testing of the plasma pool and this is the only sample that is available to the OMCL for their independent testing.

3. POST-POOLING INFORMATION (restricted session)

The following question was addressed in the restricted session:

- *The Note for Guidance on Plasma-derived medicinal products requires that “Where there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A, B or C, the case should be referred to the relevant Medicines Competent Authority(ies)...”. Have referrals been made and how were they dealt with?*

The discussion showed that OMCLs have different experience with post-collection information with some receiving reports while others have not. It was suggested that, in addition to the requirement for immediate referral to the authorities, information is provided in the PMF annual update.

4. IMPACT OF CHANGES IN THE EUROPEAN LEGAL ENVIRONMENT (restricted session)

4.1 In vitro diagnostics

M. Nübling described the change in the control of tests for viral markers as a result of the implementation of the *In Vitro* Diagnostic Medical Devices (IVD) Directive. He addressed the following questions:

- *What impact has the changes in the European legislation for in-vitro diagnostics on the assessment of the safety of blood products?*
- *What impact has the changes in the European legislation on national controls of test kits?*

Tests for HIV, HBV and HCV are in the highest category for evaluation (Annex 2, list A). These tests have to be evaluated by a Notified Body for CE-certification. Accreditation authorities within the Member States are responsible for the accreditation of Notified Bodies for their competence to evaluate these tests. The national Competent Authorities are responsible for the vigilance system for marketed devices.

- *What is the current situation with Common Technical Specifications?*
- *What consequences arise from this for the requirements on the test kits used for the control of the starting material blood, plasma and plasma pools?*

Tests used for plasma pool testing only fall within the IVD Directive if they are intended by the manufacturer to be used for this purpose. In-house assays are excluded. Requirements for the tests are specified by Common Technical Specifications. These specifications can rapidly be updated to reflect test improvements, epidemiological changes, availability of samples and “state of the art”. Seroconversion panels are now available and are used for performance evaluation. CE-marked IVDs represent “state of the art” IVDs in Europe. “State of the art” is guaranteed by compliance with Common Technical Specifications, performance evaluation in

direct comparison to an established device (the new test may not be worse), and the possibility of re-evaluation by Competent Authorities. The Common Technical Specifications consist of test-specific principles and minimal requirements to be met, and they also define the number and type of specimens to be used for the evaluation of new IVDs (diagnostic trials). Furthermore, the IVD Directive prescribes general quality features of assays (Essential Requirements) and features of Quality Management systems to be installed at IVD manufacturers. The requirements for the serological tests focus on assays used for testing of individual donations (according to the instructions for use), and there is no respective counterpart for the use of those assays for the investigation of pooled plasma.

At present, both national approvals and CE-certifications are allowed during the first transition phase. The second transition phase starts on 7 December 2003 when nationally approved test kits can still be on the market. All IVDs on the market will have to be CE-marked by 7 December 2005.

- *Is there a need to change the PMF headings accordingly?*

Information on tests for viral markers is requested as part of the Plasma Master File. For tests that are CE certified, confirmation of the certification is sufficient for the use of assays according to the instructions for use (i.e. for individual donation testing). There are no common validation protocols or biological standards for the evaluation of assays that fall outside of the IVD Directive e.g. “in-house” assays and antibody assays used for plasma pool testing.

There was a discussion on what information should be required for assays that were not CE-marked because they were used for testing individual donations of blood/plasma before import into the EU. If tests were not CE-marked, then validation data could be requested to demonstrate that the tests were comparable to “state-of-the-art” tests available in the EU.

4.2 The role of the Council of Europe

K-F Bopp gave a presentation on the role of the Council of Europe with respect to blood and blood components. This role is based on the principles of non-commercialisation of substances of human origin and protection of donors and recipients. Work is undertaken in two committees, the Committee on Blood Transfusion and Immuno-haematology (SP-HM) and the Committee on Quality Assurance in Blood Transfusion Services (SP-R-GS). The steering committee is the European Health Committee which meets twice per year.

The Council of Europe is involved in policy advice, standard setting, monitoring and field action. Standards are set by Recommendation (95) 15 on the preparation, use and quality assurance of blood components. The guide to the preparation, use and quality assurance of blood components is a technical appendix to the recommendation, which is updated annually.

Article 152 of the Amsterdam Treaty of the European Union requires measures for the EU to be adopted for setting high standards for quality and safety of organs and substances of human origin, blood and blood derivatives. Standards for blood and blood derivatives are being taken forward in the Blood Directive² that is currently in a Co-Decision Process. The nature of future interactions between the EU and the Council of Europe with respect to this Blood Directive is still to be defined.

K-F Bopp was asked what was the basis for the Council of Europe recommendation for non-remunerated donors. He responded that it is based on the ethical principle of non-commercialisation of the human body.

4.3 Blood directive²

As part of the Workshop, DG Sanco G/4 requested a scientific view on the following issues:

- *What are the advantages and disadvantages of including plasma for the manufacture of plasma-derived medicinal products within the proposed Blood Directive?*
- *Whether the use of non-remunerated donors is important for the safety of plasma-derived medicinal products.*

² Proposal for a European Parliament and Council directive setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Council Directive 2001/83/EEC

Discussion commenced in the Workshop and was continued in the BWP after the Workshop. A response was provided to the European Commission.

5. EXPERIENCE OF THE INSPECTION SERVICES WITH INSPECTIONS OF BLOOD/PLASMA COLLECTION ESTABLISHMENTS AND COMPANIES MANUFACTURING BLOOD PRODUCTS WITHIN THE EU AND OUTSIDE THE EU WITH RESPECT TO THE PREPARATION AND CONTROL OF THE STARTING MATERIAL (blood and plasma, plasma pools)

During the restricted session, inspectors from Austria, Germany, UK and Sweden reported on their experience and addressed the following questions:

- *What experience is available (numbers of inspections per country, involved inspectorates, what is inspected, what are the reasons for inspections)?*
- *What specific experience is available for inspection of donation centres and companies fractionating blood products with respect to the manufacture and control of the starting material (blood and plasma, plasma pools)?*

H. Kurz from Austria pointed out that the PMF is an important and central document for approval, batch release, inspections and certificates for import of blood products. In his presentation, he focused on the situation with the trade in blood and plasma derivatives. There is a need for a clear and transparent control system during the whole production chain, starting with the collection of blood or plasma, through testing, storage, and fractionation, until the finished product. There should be controls on import and export of plasma and fractionation products and on the distribution of plasma-derived medicinal products (need for inspection and licensing at every point). A data-exchange system should be in place including a rapid alert system to inform all interested parties within the EU on deficiencies.

J. Neuhaus described the German situation. Before plasma, plasma intermediates or plasma-derived medicinal products are imported into Germany from third countries (i.e. outside EEA), inspection of collection centres, testing centres, storage and production facilities is performed. In Germany designated inspectors, who have specific experience in this field perform these inspections. Experts from the competent authority responsible for the approval of blood products usually accompany the inspectors. According to his experience of inspections in the US, approximately 20% of centres have critical deficiencies leading to refusal of the particular centre, another 20% have major deficiencies. Sometimes centres that have been found acceptable are found to be not acceptable two years later. He concluded that it is necessary to inspect centres and test labs in the US at least on a two-yearly basis, and to inspect each individual centre of a group. It is impossible to rely on questionnaires or other information supplied by a company to conclude on compliance and it is important to cover the whole supply chain from plasma collection via testing, storage and transportation to fractionation.

D. Kruger confirmed from her experience the necessity to inspect each individual collection centre, even from the same organization. Besides the collection centres, also the testing centres and the establishments for storage and distribution have to be inspected. However, there is a shortage of inspectors and resources. She also explained the need for harmonization of the inspection requirements and the need for transparency. A pan-European centralised inspection system would be an improvement. Standardisation of inspection is a key element for mutual recognition of inspections. The inspectors should be experienced in the inspection of blood and plasma collection establishments; training on the job should be foreseen. As an aid to standardisation, there are already a number of documents available concerning inspections:

- *EU Guide to Good Manufacturing Practice (GMP), Annex 14*
- *PIC/S³ GMP guide for blood establishments, 2001*
- *Site Master File (SMF, based on PIC SMF)*
- *Questionnaire (PIC/S Aide-Memoire for the inspection of blood donation and plasmapheresis centres, 1997)*

³ Pharmaceutical inspection convention scheme

- *Inspection report format (EMEA).*

In this context, she referred to the PMF as an important document for the inspectors, as it contains information relevant for inspection and is updated annually.

The intervals between inspections must not be too long, because of frequent changes

- In the blood/plasma collection centres supplying plasma to the fractionator
- In the test labs used by the blood/plasma collection centres
- In the test kits used by the test labs
- Frequent procedural and personnel changes in the centres.

M. Kavanagh described the change in 1998 from UK plasma to US plasma for the manufacture of UK-produced plasma-derived medicinal products. All testing centres and most collection establishments supplying plasma for the manufacture of these products have been inspected. He reported similar experience to the German inspectors with respect to the findings and due to this he confirmed that inspection is considered necessary. Because of the shortage of inspectors, it is not possible to inspect all US centres whose plasma is used in the manufacture of products authorised in the UK market. He suggested a two-year algorithm of repeated inspections.

F. Fritzson described the Swedish situation. In Sweden, a database exists on the sites to be inspected and the inspections performed. He supported the suggestions made by the previous speakers to share the information on rejected and accepted establishments between the EU Member States.

The following additional questions were addressed:

- *How is the collaboration between inspectorates and approving authorities working?*

In most countries there is a close co-operation. In this context, the PMF was considered as an important and central document for all parties involved in approval, batch release, inspections and certification for import of blood products.

- *How is the PMF used and what should the future approach of the PMF be from an inspector's point of view?*

The PMF is already used by inspectors as a reference document for inspection of collection and testing centres. Since it may take up to 5 years from donation until release of the product, the PMF needs to contain information relevant to that whole period and not just the situation at a specific date. It also needs to be updated frequently to include the latest information.

- *What are the findings with respect to the manufacture and control of the starting materials (blood and plasma, plasma pools)?*

Typical reasons for rejection are: donor suitability determination, donor identification, immunization programs, apheresis and disconnection, plasma processing (sampling), insufficient freezing conditions, unresolved freezer temperature excursions, insufficient segregation of untested, released, specialty and compromised plasma, plasma release related issues, incorrect or not timely performed look backs, problems with removal and destruction of suspect units, training of personnel.

Major problems with test labs include: maximum time between donation and testing is exceeded, risk of cross contamination during uncapping of the sample tubes, use of external controls (for test kits), plasma receipt procedures.

- *What should be the approach to inspecting collection centres and testing sites?*

There is a need for harmonisation of inspection requirements. Several documents could contribute including the PMF. Inspections should be performed at regular intervals and inspection every 2 years was considered appropriate. The possibility of a pan-European inspection system should be discussed to share the responsibilities, personnel and expenses.

- *Should every collection centre be inspected when inspecting collection centres outside the EU?*

Experience has shown that there is a need for inspection of all collection centres. Testing sites should also be inspected. However, inspection resources are limited and inspections are not yet performed for all centres supplying blood or plasma to the EU.

6. QUALITY SYSTEMS IN INDUSTRY (open session)

6.1 PPTA Europe plasma quality systems and initiatives

G. Zerlauth described the PPTA system, on behalf of B. Whitaker. In 1991, PPTA initiated two quality initiatives: QSEAL (Quality Standards of Excellence, Assurance and Leadership) and iQPP (international Quality Plasma Program), based on standards for collection centres, donors, donations and quality. The first audits to control the concerned collection centres took place in September 2000 and the first certificates would be awarded in November 2001. The system is based on four global voluntary standards: qualified donor standard (ensure committed healthy donor population), viral marker standard (demonstrate quality of donor population), NAT testing standard (NAT testing for HIV, HBV and HCV for early detection of these viruses) and inventory hold standard (60 days subsequent to donation; permits retrieval of plasma prior to use). Upcoming standards are parvovirus B19 testing, standards for intermediates and standards for plasma derived from whole blood. For parvovirus B19, NAT testing will start no later than 31/12/2001. Plasma that would result in a manufacturing pool exceeding 10^5 IU/ml will be removed.

6.2 EPFA plasma quality systems and initiatives

J-N. Colin described, on behalf the EPFA Regulatory Working Group, the EPFA quality systems for recovered plasma and explained that standards already exist within their national organisations. They pointed out that the strength of this system lies in individual and mini-pool testing, a strong link with haemovigilance and post-transfusion surveillance, unpaid donors from low risk population, regulation/inspection by national competent authority, and (for some of them) introduction of NAT testing and nanofiltration.

Current initiatives of EPFA include the collaboration with EBA (European Blood Alliance), harmonisation of standards for recovered plasma and a shared data collection system (e.g. epidemiology). T. Najdovski presented the EPFA initiative for harmonisation of standards for recovered plasma. Standards already exist within their companies; however, there is a need for harmonisation and communication. The scope is to have a common harmonised approach on the reference documents, common view on legislation, a harmonised strategy and a communication platform. They are working on:

1. Recovered plasma specifications.
2. Donor & donation qualification: medical examination by medical doctor, standardised questionnaire (document will be prepared in near future); the use of first time donations will be examined.
3. Post donation information: cellular components are used before plasma for fractionation is used.
4. Registration and certification.
5. Post transfusion surveillance.

As part of the discussion, EPFA indicated that most of their member companies have an inventory hold period to prevent big losses of valuable material.

The following questions were addressed:

- *What is the scope of these measures and what impact is expected from these measures on the overall safety of blood products?*
- *Is there a need to require these measures generally?*
- *Are there any other measures planned in this field?*
- *How to implement these measures into the PMF headings?*

Both EPFA and PPTA are working on the implementation of quality systems, which to some extent differ, due to the differences in donor-population. The present careful selection of a low risk donor population and the testing currently in place are essential in achieving the safety of the plasma supply. The quality systems established to ensure quality, safety and traceability of the donations should be described in the PMF. Therefore, the headings need to be amended accordingly.

7. REPORTS OF EPIDEMIOLOGY OF BLOOD COLLECTING CENTRES/ ORGANISATIONS AS PART OF THE PMF (open session)

G. Werner and P. Zorzi-Morre reviewed their practical experience with the assessment of epidemiology data provided in the PMF. Both identified the need to completely revise the guidance. The wording, terminology and presentation of epidemiological data are currently highly variable between PMFs and even within one PMF. At least it is necessary:

- To specify the format of data presentation
- To define whether donors or donations should be used as the reference for the collection of epidemiological data
- To define the donor population (e.g. applicant, repeat donor)
- To define the expression of marker rates and to clarify whether data are required for the individual collection centres
- To establish a reference database to control/assess the data provided.

The scientific basis for the assessment of the reported epidemiological data needs to be established, since “high risk donor population for blood-borne infections” as currently specified in the PMF, is not sufficient to allow a harmonised assessment. The donor definitions in the EU Council Recommendation on “The suitability of blood and plasma donors and the screening of donated blood in the European Community”, 98/463/EC, should be taken into account. In addition, it was considered important to discuss consequences of non-compliance with defined requirements for the epidemiological data reports.

Both speakers made specific suggestions on various aspects.

The representatives of the manufacturers (C. van der Poel for EPFA, G. Schreiber for PPTA (also presenting on behalf of B. Whittaker)) referred to specific methodological aspects of epidemiological data collection, which differed in their content, criticisms and proposals. It was identified that the crucial point was to find a method to demonstrate that manufacturers do not collect plasma from a high-risk population. Clarification is needed as to the definition of a “high risk” population, “residual risk” and “incidence trends” for the donor population. EPFA emphasised the importance of prevalence and incidence data for the donor population (with calculations on a donor basis). In contrast, PPTA’s approach using the Viral Marker Standard focused on donations.

The following questions were posed in this session

- *What should be the requirements for the reports on epidemiology of blood collecting centres/organisations as part of the PMF?*
- *How should donor populations be defined and categorised and expression of marker rates be harmonised?*
- *What should be the scientific criteria for assessing the acceptability of the donor centre with respect to the reported epidemiology?*
- *What should the consequences be if there is non-compliance with defined requirements for epidemiology?*
- *How should the incidence of seroconverted donors be reported to the competent authorities?*
- *How to address the difference in the frequency of donations between blood donors and apheresis donors?*

There was common agreement on the importance of the exclusion of collection of blood or plasma from a high-risk population for the safety of plasma-derived medicinal products. However, it was recognised that these key questions could not be resolved as part of this workshop. The proposal to convene a specific working group to establish the scientific basis to answer the questions was unanimously accepted.

8. CRITERIA FOR THE ASSESSMENT OF THE PMF DATA AND CONSEQUENCES OF ASSESSMENT (open session)

8.1 Content of the PMF

The following questions were addressed:

- *What should be the content of the PMF and how should it be used?*
- *What changes should be considered for the review of the headings of the PMF?*

J-N Colin (EPFA) proposed that NAT should now be considered as a normal routine method and should not be treated separately from the others tests. The global strategy against each major virus, from the donation to the pool, should be emphasised. He considered that the proposed annual checklist could be a useful tool for traceability of modifications to the PMF.

The possibility to refer to accepted standards and requirements of other competent authorities (FDA, USP) was considered as essential by B. Glantschnig (PPTA representative). For example, reference is often made to *in vitro* diagnostic tests or blood bags meeting US/FDA standards. She also proposed that plasma pool preparation should be either part of the PMF or of the medicinal product dossier (but should not be duplicated in both documents). Various other proposals to reduce some of the detail in the PMF were presented.

E. Voets presented the experience and views of a competent authority. She indicated that the level of detail to describe the criteria for selection/exclusion of donors should be determined. Should all the questionnaires be included? Should specific exclusions by individual member states be included (e.g. vCJD: exclusion of donors staying in the UK)? In the case of screening tests for viral markers, it should be clear from the table, which tests are used, by which laboratory working for which transfusion centre.

8.2 Legislative proposal for the PMF

It was not the purpose of the Workshop to consider the proposed legislation for the PMF. Nevertheless, the opportunity was taken to have an update from M. Robert (European Commission) on the legislative proposal that was in development.

The presentation and subsequent discussion highlighted the following:

- Are there circumstances where it may be better for a manufacturer to have more than one PMF?
- Who should be responsible for the PMF?
- Whether there should be the possibility of assessment through either a centralised procedure or mutual recognition procedure
- The place of the PMF in the assessment of other health products (e.g. medical devices).
- How will the annual update be dealt with?
- The need for a simplified notification for minor changes.

9. CONCLUSIONS

The conclusions, recommendations and points for further action arising from the Workshop can be summarised as follows:

9.1 Tests for viral markers

- Competent Authorities wish to have mini-pool and plasma pool testing strategies described in the PMF. The question of whether mini-pool testing should be regulated was discussed. Manufacturers consider that these strategies should remain their responsibility provided that the overall objectives for quality and safety of the resulting medicinal products are achieved.
- The proposal to no longer require testing of plasma pools for hepatitis C antibodies would be considered by the Biotechnology Working Party (BWP).
- Competent Authorities considered that it would be useful to develop harmonised guidance/standards for the validation of plasma pool testing for HBsAg and anti-HIV for use by companies and OMCLs. High dilution sensitivity is important for such pool testing.
- The BWP will give further consideration to the information that will be required in the PMF where non-CE marked tests are used for testing of blood/plasma donations (e.g. tests used exclusively outside the EU). The information supplied should establish that these tests are not inferior to the “state of the art” for CE-marked tests in the EU. Guidance would be provided in the PMF guideline.
- The proposed use of proficiency schemes for manufacturers’ NAT testing and regular reports in the annual update of the PMF should be further explored.
- It would be useful to publish the substantial experience of OMCLs with plasma pool testing.
- The BWP would consider whether post-collection information (indicating that a donation contributing to the plasma pool was infected with HIV, hepatitis A, B or C) should be included in the PMF annual report in addition to immediate reporting to the Medicines Competent Authorities.

9.2 Inspection of sites for collection, testing and storage of blood and plasma

- Inspection of sites for collection, testing and storage of blood and plasma is considered an important part of the established measures to ensure safety of plasma-derived medicinal products.
- Harmonised guidance and training for inspectors is important. The EU GMP guide, PIC/S documentation, the Inspection report format and the Plasma Master File contribute to a harmonised approach.
- There is a need for improved controls on import, movement/processing within the EU, and export of blood and plasma to prevent fraudulent global trade (need for inspection and licensing at every point).
- The following issues would be referred to the Ad-Hoc GMP Inspection Working Party:
 - The shortage of specialised inspectors for undertaking inspections outside the EU. The large number of centres to be inspected is a problem, especially since there is no mutual recognition of inspections between the EU and US. In addition, new countries (e.g. Central and Eastern European) are expected to be used for the supply of source material for the production of plasma-derived medicinal products in the near future. There is a need to improve the inspection network and resources.
 - The need for a uniform strategy for inspection of sites outside the EU (number of sites to be inspected and frequency of inspection).
 - The recommendation from inspectors to regularly inspect all sites seems to be incompatible with the shortage of specialised inspectors.
 - The need to share information between Member States on rejected and accepted establishments.

9.3 Industry Quality systems to ensure quality, safety and traceability of plasma donations

- There are differences between the quality systems for PPTA and EPFA which reflect a difference in starting material, mainly plasmapheresis (PPTA) and whole blood donations (EPFA). PPTA has established a harmonised quality system, based on common standards agreed by their members, and is in the process of implementing this. Quality systems are operating at the national level for EPFA members. EPFA and EBA are currently working on harmonised standards.
- The PMF should include a description of the quality systems used.

9.4 Epidemiology

- It was agreed that a BWP Joint Working Group involving EPFA and PPTA would be held to further develop proposals for the presentation of epidemiological data in the PMF.

9.5 PMF structure

- The PMF will be included in legislation and changes to the PMF categorised in revised variations' legislation. Although the purpose of this Workshop was not to consider the proposed legislation, a number of points for further discussion were identified. The BWP would provide their scientific input into this discussion.
- Guidance is needed on the information required when non-European standards are used (e.g. for in-vitro diagnostic tests and blood bags).
- Specific comments on the PMF content would be taken into account in the revision of the Note for Guidance on the PMF.

9.6 Blood directive

- The BWP would provide feedback to the Commission on the two questions raised by DG Sanco.

Post-meeting note: A CPMP Position Statement on “Non-remunerated and remunerated donors: safety and supply of plasma-derived medicinal products”, EMEA/CPMP/BWP/1818/02, 30 May 2002 has been published on the EMEA website.

(<http://www.emea.eu.int/pdfs/human/press/pos/181802en.pdf>).

WORKSHOP ON PLASMA MASTER FILE

Start: Wednesday 10 October 2001 at 2pm

End: Thursday 11 October 2001 at 4pm

EMEA, 3rd floor, Meeting Room 3A
7, Westferry Circus, Canary Wharf, E14 4HB

Restricted sessions: Wednesday 10 October 2pm-6.30pm
Thursday 11 October 3pm-4pm

Open session: Thursday 11 October 8.45am-3pm

(Restricted sessions were for BWP members and experts, OMCL experts, Inspectors, Commission and EDQM only)

List of Participants

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- Speakers:**
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