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Pre-authorisation Evaluation of Medicines for Human Use

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**REPORT OF
PMF EPIDEMIOLOGY WORKSHOP with INDUSTRY**

EMEA, 30-31 March 2009

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INTRODUCTION

The requirement to collect epidemiological data on blood transmissible infections¹ is intended to obtain information on the infection risk in a specific donor population and is thus an essential part of the measures taken to ensure an adequate selection of donors of blood and plasma. The purpose of these data is to characterise the donor population with respect to infection risk, and to allow comparison of risks between donor populations of individual collection centres. This is one of the measures to ensure that donations do not come from donors with a high probability of being infected with blood transmissible agents. Continuous epidemiological evaluation at individual blood/plasma collection centres together with an annual update of the assessment is therefore required.

Data on incidence and prevalence of transfusion transmissible infectious markers in donors of blood and blood components are also required as part of the annual reports of blood establishments (Annex II of Directive 2002/98/EC).

In light of the experience with the use of the Guideline on Epidemiological data (EMEA/CPMP/BWP/125/04, published in January 2005 <http://www.emea.europa.eu/pdfs/human/bwp/012504en.pdf>), a group of experts was assigned to critically look at the:

- 2006 submitted Plasma Master File (PMF) epidemiological data, in conjunction with the CHMP Epidemiological guideline
- 2006 and 2007 PMF evaluation reports for the relevant PMF

Feedback on this critical analysis had been provided to the PMF Drafting Group and to BWP/CHMP. A proposal for a Workshop with Industry was agreed which took place on 30-31 March 2009.

AIM OF THE WORKSHOP

In 2007, the BWP considered that there was a need to have a Workshop together with PMF holders on the experience with epidemiological data in PMFs. The aim of a Workshop would be to develop a harmonised approach amongst PMF holders on the reporting and presentation of PMF epidemiological data.

This Workshop was developed based on the experience gained in handling the evaluation of the dossiers that have been submitted to the EMEA for a PMF certification. It was intended to provide feedback and additional guidance to PMF holders on the findings and the conclusions from the critical analysis of the Epidemiological data presented to date.

ISSUES FOR DISCUSSION DURING THE WORKSHOP

- Concept of PMF Epidemiological data. Meaning, importance and potential implications of the Epidemiological data. Experience and Overall conclusions from the Epidemiological critical analysis carried out during 2007/2008
- Evaluation of epidemiological data. Experience on PMF evaluation of Epidemiological data during the certification procedure
- Regional requirements on donor selection and testing of donations
- Proposal for improvements and revision of the guideline
- Residual risk and alert limits

TIMING OF THE WORKSHOP

2 day workshop on 30-31 March 2009.

PARTICIPANTS

PMF holders

¹ Part III, 1.1, b(1)(i) of Annex I to Directive 2001/83/EC on the Community code relating to medicinal products for human use

PMF assessors

Epidemiology Working Group

The meeting was open to interested BWP members, PMF coordinators, evaluators and other participants from National Authorities, US, Australian and Swiss authorities.

DISCUSSION SUMMARY

SESSION 1

Meaning, importance and potential implications of the Epidemiological data.

M. Nübling, Rapporteur: J. Dodt.

Meaning, importance and potential implications of the Epidemiological data.

Regional requirements on donor selection and testing donations.

Industry initiatives

- a. PPTA – Submission of Epidemiological Data (B. Lauven, Talecris)
- b. IPFA -Viral Marker Epidemiology and Geographical Spread (S. Jenkins, BPL)

The scope of this session, chaired by **M. Nübling**, was to introduce the subject of “epidemiological data in the PMF”. In light of experience gained with the application of the guideline on epidemiological data (EMA/CPMP/BWP/125/04) a critical analysis of the data provided in PMF dossiers was performed for data of the last 3 years. Based on this analysis a revision of the guideline is proposed to extend the guidance to PMF holders with respect to submission of epidemiological data, critical analysis of the epidemiological data and the residual risk estimation. The intention of the first session was to introduce the subject of the meeting and to present general observations made during the recent years of collection of epidemiological data.

Presentations

The chairman, **M. Nübling**, gave an introduction on the reporting of epidemiological data including the importance of these data for the safety of blood and plasma products. The legal requirements for testing of blood and blood components for transfusion as well as plasma for fractionation were pointed out. NAT testing for manufacturing plasma pools, which is either based on legal requirements (HCV NAT) or is performed on a voluntary basis by manufacturers (HIV-1, HBV, B19, HAV), may reduce the viral load entering a manufacturing pool to a defined limit. However, for conclusions on the safety of final products the overall effectiveness of all different measures has to be taken into account. Epidemiological data allow the calculation of the risk that the manufacturing pool may be contaminated by a viraemic donation passing undetected into the pool. Examples were provided where the epidemiological data could also be used as surrogate markers for emerging viruses which are not associated with viral screening. Evaluation of epidemiological data over the past three years showed that there are quite different prevalence and incidence rates depending on the country of origin as well as the blood establishment collecting the plasma. Even within a certain blood establishment individual centres show a broad range of incidence and prevalence rates for first time and repeat tested donors. The presentation closed with the question which incidence rates are acceptable and how the limits should be identified.

B. Lauven (Talecris/PPTA) reported on the submission of epidemiological data from PPTA’s point of view. PPTA members have gained experience with data collection for source plasma. The data showed a broad range due to centre size and location. The identified difficulties in obtaining true incidence and prevalence data were reported and it was suggested to replace the term “incidence” by “positivity rate”. It was said that issues related to the interpretation of data seem to be related to the potential low absolute number of positive donors at centre level, lack of a meaningful comparator population for the donor population and difficulties in the interpretation of trend analyses due to the limited data set of 3 years. PPTA proposed to establish viral marker alert/action levels which would be relevant and acceptable for all stakeholders.

S. J. Jenkins (BPL/IPFA) reviewed the geographical spread and trends in plasma donor epidemiology. Data from four years taken from several source plasma suppliers and multiple centres were analysed. Based on the data, it appears that the geographical distribution of centres with low HIV, HBV and HCV rates can be in close proximity of those with comparatively higher rates. Within a single quality system the repeat donor positive rate for HCV was found to be not proportional to the first time donor rate, suggesting that the incidence was not predictable from prevalence data in the first time donor population. There seems to be no strong correlation between first time donor rates for HIV, HCV and HBV: a trend in one of these markers does not predict a trend in another marker. This is an important observation since a trend may be considered indicative for poor screening at the centres or risky behaviour of the donors. A trend analysis is considered of little value because often numbers found in individual centres are low and move up and down, and trends may be influenced more by the amount of plasma collected rather than by donor positive rates.

Discussion

The discussion was based around aspects outlined in the presentations.

K. Soldan (HPA, UK) clarified the definition of prevalence and incidence as given in the guideline, but Industry (PPTA) stated that they would like to provide positivity rates for the PMF documentation. There was some discussion/clarification regarding the relationship between measures of prevalence and measures of incidence, and how positive donations contribute to these measures.

The chairman mentioned that epidemiological data for blood establishments or countries do not reflect the situation for a collection centre. It was acknowledged that interpretation of data is difficult with a low number of positives at a centre level, but differences between blood establishments and countries are obvious and within blood establishments a broad distribution of viral marker rates for centres can be observed. Therefore, epidemiological data should be provided for collection centres. Industry questioned whether fine tuning at the centre level would improve safety of products. They were concerned that based on epidemiological data establishments or centres could be excluded from PMFs and proposed to use the data as a management tool by defining limits for investigations and/or follow-up actions. This procedure would take into account the variability of viral marker rates at an individual centre, rather than excluding centres. A focus could be the definition of alert levels which could be linked to audits, root cause analysis and corrective actions with the aim to improve the situation at the centre level.

SESSION 2

Submission of Epidemiological data

Epidemiological data reporting experience & critical analysis

Concept paper

M. Nübling. Rapporteurs: K. Abbink and E. Mathys

Current Guideline, Epidemiological project, Concept paper and revision of guideline.

Experience gained in the implementation of the Epidemiological guideline. Experience and Overall conclusions on PMF EPI data during the certification procedure. Proposals for improvement and revision of the guideline.

Feedback to industry on critical analysis of the epidemiological data in the PMF dossier. What additional guidance can be provided to industry on the findings from the critical analysis on the Epidemiological data? Collection and presentation of the epidemiological data by the PMF holders. Data reporting, analysis and assessment by the PMF holders.

Proposals for guideline revisions.

- a. PPTA – Epidemiological data reporting experience and critical analysis (B. Glantschnig, Octapharma)
- b. IPFA - Epidemiological data in small countries (R. Laub, CAF-DCF)

Presentations

The chairman, **M. Nübling**, presented the findings from the critical analysis of reporting of epidemiological data in the PMF dossier by industry since the guideline was put into place. The result of this analysis was a proposal for the revision of the guideline which provides more detailed guidance on data reporting and estimation of risk.

B. Glantschnig (Octapharma/PPTA) raised the issue that PMF epidemiological data reporting and analysis should not lead to a situation where collection centres and plasma for fractionation are considered unacceptable, while cellular blood components from the same centres are still being transfused. In her presentation the need for a central viral marker data repository and a viral marker standard with alert levels was highlighted.

R. Laub (CAF-DCF/IPFA) reported on the epidemiological data in small countries, the limited impact of 1st time tested donors in residual risk, the difficulties in the data collection and evaluation for small centres as well as the incidence in blood donors being lower than in the general population.

Discussion

1) Level of collection and evaluation of the data

Questions were asked on the level of collection and evaluation of the data. Should it be carried out for mobile sites, satellite points, fixed centres, centres in close geographical regions? With respect to the inspection status DG Sanco has provided a clear definition: inspection should be carried out on the collection centre level (smallest fixed collection site with fixed equipment and personnel). Nevertheless, with respect to the evaluation of epidemiological data, generation of meaningless results should be avoided (e.g. in case of very low incidence rates) and a higher level of collection of data might be acceptable, if justified.

2) Acceptable epidemiological levels

Points of discussion were:

What is an acceptable epidemiological level? Should it be a predefined limit or could it also be a statistically defined limit for a given population? Should it be the same for all collection sites / organisations / countries? One global standard for each virus? The risk with fixed viral marker levels is that for certain centres upward trends that stay below the defined limit might remain without critical assessment. Epidemiological data are retrospective data, how can these comply with a limit? Furthermore, a limit on epidemiological data should not result in a supply problem.

Preliminary outcome:

PMF holders should define acceptable limits in the PMF based on their own data. Defining acceptable ranges should be a trigger for action, not for rejection. EMEA will not set a limit at this moment. Continuous evaluation is considered more appropriate.

3) Evaluation and interpretation

Epidemiological data are meant to give a signal per centre and to continuously monitor the donor population. One tool for two purposes: improvement and acceptability. It can be used for the calculation of the residual risk and for follow up, but it is not directly meant to ensure the safety of the final product. Trend analysis over three previous years is difficult to interpret due to the limited number of time points, and especially in case of low incidence rates. How should centres with elevated incidence rates be dealt with? Collection centres in compliance with the PPTA system are asked to submit the epidemiological data twice a year. If a donation centre exceeds the predefined limit twice follow-up action is triggered. It is, however, not completely clear how these situations may be resolved in the end. PPTA performs alert level trigger action (steps prescribed, root cause analysis, best practice development). What will happen to plasma from centres that continuously exceed the limits? The acceptability of comparatively higher incidence rates should be based on careful evaluation, also taking into account the fact that sometimes cellular blood components are also used from the centres concerned.

4) Viral marker data repository

A global viral marker repository might help for transparency. The question remains, however, who should be responsible for such a repository (EMEA, PPTA, IPFA...)? FDA does not have access to this data. Furthermore, the data are not always reported by donation centres in a consistent manner, and the centre names are not always clear-cut. EDQM (together with the University of Utrecht) is already collecting and monitoring viral incidence rates of donors for transfusion products within Europe.

5) Calculation of incidence

Incidence rates should be based on donor years and not the number of donations in a time period.

SESSION 3

Overall safety

M. Martin, E. Lindberg, A-L. Smeds. Rapporteurs: M. Martin, E. Lindberg, A-L. Smeds.

Summary of Epidemiological data among PMF holders

Proposals for guideline revisions (examples and literature).

Reporting and critical analysis of Epidemiological data (e.g. identification and reporting of trends)

Residual risk (Infections risk of entering in plasma pool).

- a. PPTA – Overall Safety (R. Worofka, Baxter)
- b. IPFA – Viral risk assessment of plasma products: present-day practice and options for the future (J. Over, Sanquin)

Presentations

M. Martin (Afssaps, France) presented an overview of the epidemiological data provided in Plasma Master Files between 2000 and 2006. The trends in the rates of blood donors positive for HIV, HCV and HBV was presented per anonymised organisations and countries. The presentation focused on the differences observed in trends of HIV and HCV positive donor rates between USA blood banks and European countries on one hand and USA plasmapheresis on the other hand. When going into details, it was observed that the rates evolved very differently between four US Plasmapheresis organisations whereas the trends were very similar between the nine European countries studied. The trends were quite similar for New/First-time tested donors and Regular/Repeat tested donors for each of the plasmapheresis organisations studied.

Although some aspects of the data reporting in the PMF could influence the rates (e.g. not always confirmed positives until 2003, modifications of the markers of infection investigated and the kits used, changes in the list of collection centres for each organisation, modification of the definition of the two categories of donors, etc.), it seemed unlikely that the differences in trends observed between organisations adopting the same rules for donor selection and screening may solely rely on these matters. The question whether the local epidemiology or the compliance to selection criteria may account for these differences was raised.

E. Lindberg and **A.-L. Smeds** (MPA, Sweden) presented further examples of differences in viral marker rates between Europe and USA, within Europe, and between as well as within US plasma source organisations (as derived from four PMFs, renamed as “A” to “D” etc). Examples of regional variability in NAT yield, as derived from published data, were also presented.

Proposals for a revision of the guideline with regard to compilation of data as per type of collection system (blood bank, plasma source centre) within a country, where applicable, and tools for detection of new trends were addressed.

The need for justification of any use of donations from first time tested donations from higher prevalence regions was emphasised, with reference to the risk of an accompanying higher incidence, the impact of any false negatives (due to errors, etc) and the risk of non-detected infections in the chronic phase (especially concerning HBV).

Furthermore, the calculation of residual risk was discussed, where the impact of any differences in testing system and the proportion of repeat tested/first time tested should be taken into account. Thereby, the particular importance of NAT testing sensitivity (size of mini-pool/individual donation etc), for the first time tested donors, was pointed out.

R. Worofka (Baxter/PPTA) talked about the “safety tripod” for plasma derived products characterised by the suitability of donors, the testing of donations/plasma pools and the pathogen reduction procedures in the manufacturing process. A harmonised industry wide procedure for the reporting of data and the establishment of alert levels for HBV, HCV and HIV was supported. The same approach for source plasma as well as recovered plasma was proposed. Regarding submission of trend analyses it was pointed out that on a single collection centre level the evaluation of trending may not be meaningful (small donor population, small absolute number). Estimation of residual risk according to the method described by Westat, or a similar approach, taking into account the impact of first time tested donors, inventory hold and NAT testing in mini-pool was claimed to be very suitable for the needs of fractionators. A common approach was requested.

J. Over (Sanquin/IPFA) presented a paper prepared in collaboration with the Julius Centre, University Medical Centre Utrecht, NL, on the development of a probabilistic model for calculating the viral transmission risk, based on actual in-house data, when available, and on assumptions based on literature data or expert opinion. All aspects of the production processes for plasma products relevant to the viral risk were taken into account (e.g. plasma donation volume and frequency, ratio of recovered and source plasma, epidemiology of all viruses concerned, sensitivity of virus screening tests, inventory hold periods, formulation of batches, etc.). All data available was incorporated into a model for plasma derived products manufacture, taking into account the uncertainties of all these parameters using Monte Carlo simulation techniques. The outcome of the model consists of the estimation of the probability that a final product container is contaminated with an infectious viral particle and of the dispersion characteristics of the probability. The probability of viral contamination of a finished product, as calculated by this probabilistic model, was 0.5 – 2 logs lower compared to the conventional deterministic “worst case” approach, dependent on the respective virus (HIV, HCV, HBV, HAV and parvo B19). A sensitivity analysis revealed that the virus reduction factor of the manufacturing process had by far the largest impact, while inventory hold period, recovered versus apheresis plasma, and plasma pool size had less impact. The model as presented is published as a paper: M.P. Janssen *et al.*, *Transfusion* 48: 153-162, 2008.

Discussion

In the following discussion, several speakers expressed their appreciation of the work presented by Dr Over. However, it was noted that the aim of the Epidemiology guideline is to deal with the safety of plasma pools with regard to the epidemiology of the blood/plasma donor population and not with the risk for the finished product to transmit blood-borne viruses which is covered by the Guideline on “assessing the risk for virus transmission” (CPMP/BWP/5180/03). Regarding this matter, it was underlined that the choice between the “probabilistic” and the “deterministic” models was already debated during the preparation of the Guideline on “assessing the risk for virus transmission”. It was then considered that the deterministic model was easier to manage than the probabilistic model and provided a risk value relatively close to the upper limit of the confidence interval determined by the probabilistic model.

In the discussion that followed the Overall safety session, strategies for defining alert levels for prevalence and incidence were discussed. No one opposed to the need for alert levels, but some speakers preferred common alert levels, regardless of the epidemiological situation, whereas others argued for alert levels that would discriminate for any new trends for each organisation studied. Some speakers also commented that the actual residual risk of a non-detected infectious donation entering the plasma pool would be reduced by an inventory hold practice.

It was also noted that the epidemiological data used in the presentations in this session were reported from different backgrounds: the presentations made by PPTA were based on rates reported for individual collection centres whereas the presentations by Epidemiology Group members were based on rates for complete organisations (combining many collection centres). The small absolute numbers of positivity at the collection centre level may result in a rate with a low informative value, whereas

the accumulation of positivity of the collection centres from the same organisation may result in a more meaningful rate.

SESSION 4

Proposal for Methods/models to calculate residual risk

Risks estimates table

K. Soldan. Rapporteur: K. Soldan

Elements to be considered for calculation of residual risk estimations. Need to make a standard risk assessment to compare epidemiological data. Presentation about different methods used by PMF holders to calculate residual risk, correction factors for HBV

Concept viral alert limits and measures

Monitoring Viral Incidence Rates: Tools for the implementation of new EU regulations

- a. PPTA – A proposed metric, Alert Levels, for assessing PMF holders' source and recovered plasma collection centres for HIV, HCV and HBV (G. Schreiber, Westat)
- b. IPFA – Presentation on Incidence Monitoring Models (B. van Hout, Utrecht University, on behalf of Sanquin/IPFA)

The presentation by **K. Soldan** (HPA, UK) set-out a proposal from the Epidemiology Group for methods to be included in the Guideline (BWP/125/04) for the estimation of risk of infectious donations entering the plasma supply.

Discussion

The discussion included a question about how the resulting estimates would be used. K. Soldan suggested that besides the aim as stated in the guideline to enable comparison of donation safety between PMFs, by manufacturer/country and by time period, use of the risk estimates needed to be considered along with the question of viral alert limits. The important impact of inventory hold on the risk of infectious donations entering plasma pools was also discussed, and whether this risk reduction measure should be considered in the risk estimate method. This could be included; however, as this is not a universally applied measure, and the data to measure its impact may be variable in quality, its inclusion would potentially affect the comparability of the risk estimates as measures of donation safety based on donor epidemiology, which is the objective of this guideline.

G. Schreiber (Westat, on behalf of PPTA) presented a method for setting viral alerts proposed by PPTA, followed by discussion.

It was explained that the method presented was not the standard in use but a proposal to meet the group's objectives. There was discussion about the choice of a relatively high alert level, with a 99.5 % probability that a given centre exceeds the limit only by chance. This reference probability is chosen to assure that only a non-by-chance number of positives at a given centre is highlighted as violating the alert level. There was also discussion about the use of data from all centres to set the alert level for every centre, meaning that centres with lower rates of infection could see very marked increases in infection rates amongst the donors without triggering the alert limit. The method was considered an approach of detecting rates well above the overall average rate, and triggering PPTA action to investigate such high rates.

B. van Hout (Utrecht University, on behalf of IPFA) reported on the Sanquin/IPFA methods for monitoring incidence, followed by discussion.

Discussion included comparison of the objectives and methods of this work with that of the PPTA approach (previous presentation). This method is more sensitive to variations between centres and times. It is technically more difficult to run. More development and implementation work is in progress.

It was noted that the group should be aware that the donor epidemiology may shift and risk estimates may vary due to factors that are controlled by PMF holders but also due to factors that are not under the control of PMF holders.

SESSION 5

CoE Blood Transfusion activities

M. Janssen (Utrecht University)/J.-M. Spieser (CoE). Rapporteur: B. Ekermo

Practical experience on evaluation of Blood Transfusion epidemiological data over the period 2001-2007.

M. Janssen (Utrecht University) and **J.-M. Spieser** (CoE) reported that the Council of Europe (CoE) has performed a survey since 1989 (annually since 2001) on the collection, testing and use of blood and blood components in Europe on a regular basis through an adapted questionnaire to Member States representatives. The preliminary results of an analysis of observed infections amongst first time and repeat tested donors for HIV, HCV and HBV are currently available for the years 2001 to 2007. During the years 2001 to 2005 complete data exist for 21 member states of the Council of Europe, while data from 25 member states are lacking for one or more years. Confirmed positive test results in repeat tested donors are considered as ‘‘incidence’’, while results from first time tested donors are considered as ‘‘prevalence’’. The preliminary findings are:

- **strong regional differences** in incidence and prevalence (ranges per disease from a factor 100 to 10,000)
- **Increase in HIV incidence** amongst repeat donors (0.2 per 100,000 donor years per year) **and prevalence** amongst first time donors (0.5 per 100,000 donor years per year)
- **Decrease in HCV incidence** amongst repeat donors (0.8 per 100,000 donor years per year) **and prevalence** amongst first time donors (15 per 100,000 donor years per year)
- **Decrease in HBV incidence** amongst repeat donors (1.3 per 100,000 donor years per year) **and prevalence** amongst first time donors (10 per 100,000 donor years per year)
- **Trend results strongly depend on inclusion and exclusion criteria used and vary per region**

Since 2007 the survey is web-based, and since then 1½ years’ responsibility for data collection has been transferred to European Directorate for the Quality of Medicines & HealthCare (EDQM, website www.edqm.eu)

In conclusion, for the time being the data can only be considered preliminary/experimental. The aim was to get 100% coverage, and also to get comparable data with respect to sensitivity of test methods used etc. In future, close communication between EDQM and the EMEA Epidemiology working group was considered to be useful.

Close of meeting and next steps – Revision of the guideline and publication for external consultation – M. Nübling. Rapporteur: M. Stierschneider

PRESENTATION BY M. NÜBLING ‘‘PMF EPIDEMIOLOGY WORKSHOP’’

M. Nübling summarised the key points of all presentations.

NEXT STEPS (S. DOMINGO, EMEA)

S. Domingo introduced the next steps. Further discussions at EMEA level will be necessary; the revision of the Epidemiology guideline is currently in progress.

Timelines for the Revision:

May/June: Publication of guideline on EMEA website

Consultation phase: 3 months for consultation, August deadline for external comments

Comments discussion by PMF Drafting Group/BWP

Finalisation, CHMP adoption and publication: planned for end of 2009/beginning of 2010