25 February 2016
EMA/651460/2015

Overview of comments received on 'Draft Revision of the Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	International Plasma Fractionation Association (IPFA) Our reference IP-15-172
2	Sanquin
3	Kedrion
4	Octapharma Pharmazeutika Produktionsges.m.b.H
5	PPTA

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
1	1 welcomes the opportunity to comment on the Draft revision of the Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008) following the EMA/CHMP/BWP/295676/2014 Concept paper and the Expert meeting which was held in November 2014. The revision reflects the discussions and outcomes of the meeting and provides clarification on important issues such as Definitions of Centres, Epidemiological data requirements for approval of blood establishments. 1 nicely welcomes that the revision reinforces the EMA view that the aim of collection and analysis of epidemiological data is monitoring and quality improvement (CAPA) of collection centres as part of the quality system for the manufacture of plasma products, considering the contribution of major safety interventions such as donor selection, testing of donations and virus inactivation/elimination. Considered separately, epidemiology would be of limited value for the safety of plasma products. The draft revision proposes guidance on parameters such as adjustments factors, window periods… which are necessary for analysis of epidemiological data: simplifications introduced are very welcome and are expected to facilitate the preparation and the assessment of PMFs. 1 supports the view that setting different alert limits for FTD and RTD is deemed to be relevant. The introduction of definitions for the different types of centres is also very welcome. However, importantly, specificities of BE III, especially for the not for profit sector, such as potentially low number of donors/donations, same geographical area than the	Acceptable if justified. Terminology: Please note, fyi, the section 12, at the time of consultation, made reference to the RBA terms (BEI-III). This has now been revised and terms reverted to “centre and establishments”, throughout the guideline, after the EC clarification, that for the PMF, these “centre and establishment” terms are part of the PMF Regulation (also Variation regulation) and should remain to be used in the relevant PMF related guidelines. Hence, the PMF EPI revised guideline will now only make reference to centres and establishments. Nevertheless, upon the RBA is completed and published, if useful to include in the EPI guideline, a link to the RBA (for the terms BEI-III) can be included. Also, the guideline requires EPI data by country, “organisation” and centre and, now the terms used in the EPI guideline are: “centres” is used as *“blood/plasma individual collection site”* (definition in the PMF

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	corresponding BE II, same quality system,… addressed by the draft note for guidance for reporting and assessment of epidemiological data; 1 considers that upon justification by the PMF-H data from BE III could be merged with the corresponding BE II. The definition of requirements regarding epidemiological data for the addition of BE is also nicely welcomed.	Scientific requirements' guideline) and "establishment" (in the EPI guideline formerly "organisation", definition as per Blood directive *"structure body responsible.."*). Also, mentioned in the earlier paragraph, section 12 has been aligned accordingly, after consultation with EC during this consultation period in response to consultation comments.
2	This PMF-H welcomes the opportunity to comment on the Draft revision of the Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008) following the EMA/CHMP/BWP/295676/2014 Concept paper and the Expert meeting which was held in November 2014. Please, find below our comments on the draft guideline. A clear goal of the epidemiologic evaluation should be defined. It appears that it is not relevant what the incidence is, as long as it is constant over time. A clear message during the meeting in November 2014 at the EMA was that the safety of the final product should be taken into consideration. Otherwise, monitoring the epidemiology is of limited value for the plasma products.	The goal is to assure that plasma is not collected from geographical areas with particularly high incidence/prevalence. Firstly, it is given in section 3 that there is a legal requirement to include epidemiological data on blood transmissible infections in the PMF. The PMF EPI requirements are regulated in the legislation (Commission Directive 2003/63/EC of 25 June 2003, amending Directive 2001/83/EC, see PART III, Section 1.1.b) (1) (ii), "*Epidemiological data on blood transmissible infections on centres or establishments in which blood/plasma collection is carried out" is part plasma origin information required*"). Also, data on incidence and prevalence of

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		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[i]). Secondly, in section 4 the importance of the epidemiological data for an adequate selection of donors is discussed. This to assure that plasma is not collected from donors with a high probability of being infected with blood transmissible agents. Propose a slightly rewording i.e. the last sentence in section 4 moved upwards in the text. Please see the document revision Guideline PMF-EPI The PMF does not consider further manufacturing/inactivation steps specific for final products.
5	The plasma pool for fractionation is the starting material of plasma derived products; for example see EMA/CHMP/BWP/706271/2010 [Guideline on plasma-derived medicinal products], especially 9. Assessing the risk for virus transmission (former guideline CPMP/BWP/5180/03). Therefore, only the virus load in donations which is not detected or eliminated by appropriate measures (e.g. inventory hold and lookback) prior to pooling is relevant to potential virus contamination of plasma pools for fractionation.	In section 9 of the GL on plasma-derived medicinal products the focus is the risk assessment of the virus safety on the final product taking into account all measures taken to assure a safe product. In the EPI GL the focus is to evaluate the epidemiological situation for the concerned

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		donor population to assure that plasma is not collected from a high risk population. The safety measures have no impact on the epidemiology as such and should therefore not be included in the residual risk/epidemiological data analysis. Inventory hold is not a tight procedure because of release of plasma from non-returning donors. Inventory hold is an element of Overall Safety Strategy and not an element of epidemiological data.
5	The guideline seems to primarily focus on the epidemiology of recovered plasma, even though the majority of plasma-derived products are manufactured from source plasma. In addition, the guideline does not fully appreciate industry standards such as inventory hold, lookback, applicant / applicant return donors (and qualified donor standard) and NAT screening (PPTA standards), which already add to an increased safety margin prior to the virus reduction steps. These standards are not accepted as part of the overall collection of epidemiological data collection (listed in Tables of the Appendix to the guideline EMA/CHMP/BWP/174129/2009) but are “only” addressed in the Overall Safety Strategy. More specifically: • NAT testing: NAT screening seems not to be appreciated or accepted as a standard measure; an impact of the shortening of the window period is mentioned, but it is not really *accepted* as risk mitigation measure. The safety of the plasma pool for fractionation and thus, the final products, is governed by the virus load and the number of donations of infected donors below the limit of detection of the NAT assay entering a plasma pool for fractionation, taking into consideration also the inventory hold for source plasma.	It is not the intention with the GL to primarily focus on recovered plasma. For the second comment about inventory hold, look back etc please see comment above. Regarding the impact of the NAT testing for the shortening of the window period this is of course acknowledged as one measure to contribute to the safety of the final product. Within a PMF a large variety of tests and mini-pool sizes are used. To facilitate the calculation a simplified approach with proposed worst case window phases are given now in the GL. However, other window phases can be used for the calculations if justified.

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5	In Table 3 (Appendix to the guideline EMA/CHMP/BWP/174129/2009) “No. of newly acquired infections (seroconversions)” in “repeat tested donors” is required; however provision of NAT data is not addressed, which are more relevant for incidence rates.	Agree. This will be clarified in the Appendix.
5	Reporting and interpretation of “worst case” risk estimates: • These worst case assessments do not assess the donor population actually represented in a plasma pool for manufacturing (see general comment above on PPTA standards). The potential virus load in representative pool(s) should be calculated based on the result of the risk estimate(s); for this risk estimate, using “worst case” situations (e.g. different plasma sources, different testing strategies, FTT as well as RT donors) described and justified by the applicant, the risk-reduction measures such as inventory hold, look-backs, further NAT testing of manufacturing plasma pools is not to be included in the risk estimate but described in the Overall Safety Strategy. Specifically, what is described as the “worst case scenario” for the risk analysis is neither a correct application or interpretation of the risk concept. The residual risk measure was **derived to assess the possibility of an individual receiving an infected unit of blood when getting a transfusion**. However, for plasma the individual never receives a plasma component that has not been subjected to virus removal. Thus, the measure is for the probability of a possibly infected unit making it to the plasma pool and should only be used for estimating risk for donor units that can be incorporated in the manufacturing pool. In the case this removes Applicant donors and includes the impact of the inventory hold period (see PPTA standards above), both of which have been consistently demonstrated to reduce the risk of a possibly infectious unit entering the pool. The worst case situation should enable the PMF Holder to factor in	No change is proposed See also response comment 45. It is agreed that this is a worst-case situation and risk of an infectious donation entering a plasma-pool may be reduced by other safety measures in place. However, here only the epidemiological data are addressed. The safety measures have no impact on the epidemiology and should therefore not be included in the residual risk/epidemiological data analysis.

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	these factors in estimating the possible risk of having a unit entering the manufacturing pool. Any unit would have to be below the limit of the NAT detection and would enable to estimate the viral loads in the processing pool.	
5	Syntax: Appropriateness of the adjective “viral” should be verified; e.g. “viral load” is in our opinion incorrect (even if frequently used) as viral does not describe the characteristics of the load. This should be changed to “virus load”.	Agreed

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
1. Line 59	4	Comment: Different wording "HBV adjustment factor" versus "HBV incidence adjustment factor" in line 363. Proposed change (if any): line 363: 10.3. The HBV adjustment factor model	**Proposed text**: *"HBV incidence adjustment factor" throughout the document.* *This factor is applied to correct a possible underestimation of the incidence of HBV infection because markers for infection may only be present transiently. As such, the use of the term 'HBV incidence adjustment factor' seems correct.*
2. Line 63	4	Comment: Different wording for the use of control charts: in line 245 "... may assess changes ... with the use of control charts"; in line 262 "control charts may be used"; in line 264 "control charts should be submitted" and in line 274 "control charts can be useful". Proposed change (if any): Control charts mentioned throughout the whole document are seen as a possibility to present epidemiological data but are not mandatorily required to be provided.	**Proposed text for clarification**: "control charts **can be** useful" *Only applies to individual centres.* *Control charts for organisations/ countries are mandatory.* ***Line 63 has been revised**:* *"Control charts <u>or other graphical tools</u> are mandatory for organisations/ countries."*
3. Line 69	5	Comment: Testing of plasma pools (not only donations) is required by	**Proposed change not agreed** The scope of the guideline is on the scientific

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Line 83		European Pharmacopeia and Directives 2001/83/EC and 2003/63/EC. Testing and releasing of plasma pools, when non-reactive, is an essential safety measure which should be considered in the guideline. Proposed change (if any): To be added after line number 83: “Reference is also made to European Pharmacopeia and Directives 2001/83/EC and 2003/63/EC, which require testing of first homogeneous pool of plasma and releasing it only when non-reactive”.	data requirements for epidemiological data
4. Line 89	5	Comment: The term ”virus reduction” should be used instead of virus “inactivation” currently stated in the guideline. Reduction is more appropriate as e.g. virus filtration removes viruses but does not inactivate them. Proposed change: Replace “inactivation” by “reduction”.	**Agreed**
5. line 92	12	Comment: Proposed change (if any): *Add the following line:* *“Low incidence rates and low prevalence would indicate a low risk population, which can be taken into account when assessing the overall viral safety of the plasma product prepared from the*	**No change** This should be addressed at the product level and not in the PMF.

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		plasma."	
6. Line 132	5	Comment: Given the significant amount of source plasma used for manufacture of plasma-derived products (>85%), applicant return source donors, including applicant donors returning for testing a second time (as per PPTA standards) should be reported separately and not included under repeat tested donor's definition for epidemiological data reporting. Applicant donors returning for testing a second time are considered in the same category as first-time tested donors and, unless two negative donations are made the donor is not accepted. This is to ensure consistency with the statement in the guideline (lines 198-199) that "the donor population which actually donates into the plasma pool should be described". Reporting of applicant return donors, including the applicant donors returning for testing a second time under "repeat tested donors" category would result in overestimated incidence rates which will not reflect the actual donor population donating into the plasma pool Proposed change: To consider applicant return donors of source plasma, including applicant donors returning for testing a second time in the first time tested donors definition: First time tested | Person whose blood/plasma is tested for	**No change** The current concept used in the GL is to conclude about the prevalence and incidence in the donor population and to have the same approach for both source plasma and recovered plasma. However, in the evaluation of the viral marker rates for specific centres information about the number of positives related to applicant donors may be of value for the conclusion of the situation.

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		donor: the first time for infectious disease markers (with or without donation) without evidence of prior testing in a given blood system. For source plasma donors applicant return donors and applicant donors returning for testing a second time are to be considered as first time tested donors. Repeat tested donor: Person whose blood/plasma has been tested previously for infectious disease markers in a given blood system. This does not include applicant return donors and applicant return donors making their second qualifying donation for source plasma donations.	
7. Line 147	5	Comment: “Effective therapy” should be replaced with “effective vaccination” as therapy will most probably still result in seroconversion of the donor. Vaccination will more likely prevent an infection. Proposed change: Replace “therapy” with “vaccination”.	**Not Agreed** “vaccination” does not apply to HIV and HCV.
8. Line 173	1	Comment: Typo to be corrected Proposed change: …for a large numbers of donors.	**Done**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
9. Line 215	1	Comment: Data would have to be reported "…per individual collection centre" whereas in the current version, data have to be reported" per centre". While it was indeed needed to be more precise here, it should not be ignored the reporting "per individual collection centre" is relevant mainly for apheresis centres and for a certain number of donors per centre. In particular, in the case of blood establishment collecting recovered plasma from non- remunerated donors, the number of satellite centres (BE III, performing collection only – see Line 453) can be very large, the size of the centre very low, locations subject to frequent move/relocations within the same geographical area. • In some countries, all collection centres are part of one organization, operating both a nationwide quality system and a nationwide donor management system. • Donors may donate blood or blood components at various collection centres located closely to the place where they live or, for instance, at mobile centres near their work or the place of residence during vacation. A donor can donate whole blood and blood components (by aphaeresis) as well during a calendar year, depending on both his/her preferences and specific requests of the Blood Establishment. • Data should be reported per individual collection centre,	**No change** *Data should be reported per individual collection centre Reporting at another level may exceptionally be accepted if justified i.e. geographical areas where prevalence/incidence data are very low and when the size of the centre is very small. As this concerns exceptional situations this is not specifically mentioned in the GL*

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		however upon justification from the PMH-H, reporting of data at the level of regional centres and/or processing centres, should be acceptable, in particular for countries with low infection rates (e.g. France, Germany, Belgium, the Netherlands…). As the annual number of infected donors per collection centre can be very low (down to 0 or 1), epidemiologic evaluation on this level would be meaningless. Please add: "*For BE located in geographical areas where prevalence data are very low and when the size of the centres (BE III) is very small, upon justification of the PMF Holder, reporting and assessing the data at the level of regional/processing centres is acceptable.*" Proposed change : "Data should be reported per country, per organisation and per individual collection centre, and per calendar year… (Ref. EMA/219007/2015). **For BE located in geographical areas where prevalence data are very low and when the size of the centres (BE III) is very small, upon justification of the PMF Holder, reporting and assessing the data at the level of regional/processing centres is acceptable."**	
10. Line 215	4	Comment: What does collection centre mean? Unclear definitions throughout the whole document (line 125 and footnote, line 448).	*Agree to revise the guideline to be consistent.* *See comment 9.*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Data should be reported per country, per organisation and per individual blood or plasma establishment, ...	
11. Line 215	5	Comment: Given the continuously increasing amount of mobile blood collection within the blood collection organisations supplying recovered plasma and the fact that in most cases these mobile collection teams are operating directly under the “blood transfusion/processing centre (the centre responsible for separation of blood components)” and not under the fixed collection-only collection centre reporting of the epidemiological data per individual collection centre is not likely. Additional consideration should be given to the fact that epidemiological data sets are generated from the Laboratory Management System of the central testing laboratories of blood collection organizations and are grouped per transfusion/processing centre, where the tested donations have been processed. See also general comment on reporting epidemiological data for recovered plasma. Reporting and inclusion of regional epidemiological data for recovered plasma should be allowed. Proposed change: Replace ”per individual collection centre” with “per individual collection centre for source plasma collection centres and per processing centre for recovered plasma”.	**No change** *See comment 9*

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12. Line 217	1	Comment: "The data should be reported for the current year and the three previous years." *Current year* might be confusing. Proposed change : The data should be reported for the **reference period of the last Annual Update and the 3 previous years.**	**Change wording proposed** te*xt:* *"The data should be reported for the reference period of the Annual Update or initial certification and the four previous years".*
13. Line 218	4	Comment: Different time periods for reporting epidemiological data are required in different sections. Three years in line 218; >5 years in line 267 and up to 4 years in line 467. Same time period for all sections are recommended. Proposed change (if any): Change all relevant sections to 5 years.	**Agreed**. Time period has been harmonised to 5 years, i.e. the referenced period of the PMF and 4 previous years. However, for the monitoring of change (chapter 9), data from all previous years, as far as data are available, should be used for the comparison with referenced period.
14. Line 218-219	5	Comment: The proposed guideline states "If a country is collecting both whole blood recovered plasma and plasmapheresis plasma data should also be summarised separately for each of these two categories". Some blood collection organisations collecting whole blood also collect plasma by plasmapheresis technique from the same donors. Therefore, reporting of whole blood epidemiological data and plasmapheresis plasma epidemiological data will give a misleading overview by counting the same donor twice. Flexibility should be provided to report such mixed donors in the category of the plasma which they	**No need to change** *The data should not be reported twice in such situations.* *In situations where the organisation collects both type of plasma this should be clearly stated. If separate reporting of data from recovered and plasmapheresis donors is not feasible at the level of organisations or individual centres, data may be reported in the category of the plasma which are most frequently collected.*

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		donate more frequently.	
15. Lines 232-234	5	Comment: Applicant return source donors and applicant return donors making their second qualifying donation (as per PPTA standards) should be reported separately and not included in repeat tested donor calculation for incidence calculation in order to be consistent with the statement in the guideline (lines 198-199) that “the donor population which actually donates into the plasma pool should be described”. Proposed change: Not to include applicant return donors and applicant return donors making their second qualifying donation into the incidence calculation in formulas 2, 3 and 5. The sentence “For companies using the applicant/qualified donor system, this includes “applicant donors” tested for a second time, “applicant donors” requalifying after an interval of 6 months or more, and “qualified donors” should be replaced with “For companies using the applicant/qualified donor system, this includes “applicant donors” tested for a second time and “qualified donors”. Table 2 of the Appendix to the guideline (Ref. EMA/CHMP/BWP/174129/2009) should have a possibility to separately report applicant return donors from repeat tested donors. Table 3 of the Appendix to the guideline should not include applicant return donors and applicant return donors making their second qualifying donation for calculation of incidence rate (Parameters 1 and 2).	**No change** ***Please see comment above***.

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16. Line 240	5	Comment: "9. Monitoring change and alert limits…" The difference between the "upper limit" and the "alert limit", their purpose, and practical application(s) should be clarified.	**The text has been revised** and there is no more mention of upper limits. For monitoring changes graphical tools should be used which are sufficiently indicative to determine any possible trends, but statistical analysis and/or introducing upper limits in control charts are not mandatory for trend analysis. However, the alert limits to detect centres with viral markers above the acceptable range remain.
17. Line 243	4	Comment: What does "normal range" mean? Is it the range based on data from the submitted establishments or any comparative data from publications for the given donor population? Proposed change (if any): The purpose is to identify collection centres with rates of infectious markers outside the normal range for the given donor population **of a country** in the PMF and discuss any overall changes in the rates in (parts of) the donor population.	**No change** The introductory wording "*normal range for a given population*" is kept (it may be either an organisation or a country). More specific guidance is given below (lines 263-303).
18. Line 249	5	Comment: Please remove the single referenced article (Janssens MP et al, 2009). There are a number of appropriate statistical techniques for analysing trends. The PMF Holder should select the one most suited and describe its own approach in setting the limits.	**Agree**
19. Lines	5	Comment:	Line 251, which concerns an introductory

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250-251 284-286		There are no statistical approaches defined for the normal range of the donor population in the PMF. The currently used PPTA Alert Level model is based on quite broad set of data from multiple PMF Holders and represents the geographical distribution of the source and recovered plasma centres relevant for sourcing plasma for fractionation for the EU market. Creation of the “PMF-based donor population”-specific Alert Levels will not add additional safety measures and will be subject to update with every change in supplier composition of the certain PMF. The current PPTA Alert Level model provides more stable Alert Levels, as they are calculated based on a broad set of sources and centres in different regions with considerable geographic and demographic diversity. Proposed change: In line 251 replace “viral marker rates clearly outside the normal range of the given donor population(s) in the PMF” with “viral marker rates above acceptable range”; in lines 285-286 replace “viral marker rates clearly outside the normal range for the respective donor population in the PMF” with “viral marker rates above acceptable range”.	paragraph, has been slightly revised; the word “clearly” has been removed. Lines 285-286: The text has been revised and there is no more mention of upper limits. For monitoring changes graphical tools should be used which are sufficiently indicative to determine any possible trends, but statistical analysis and/or introducing upper limits in control charts are not mandatory for trend analysis. However, the alert limits to detect centres with viral markers above the acceptable range remain.
20. Line 251	4	Comment: In addition to question related to line 243 what means “clearly outside the normal range”? Either a value is outside or inside. Proposed change (if any): Delete “clearly” in the sentence.	**Agree**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
21. Lines 261	5	Comment: Same as for line number 215. Proposed change: Replace ”the individual collection centre” with “the individual collection centre for source plasma collection centres and the processing centre for recovered plasma”.	**No change** See response to comments 9-10-11.
22. Line 262	4	Comment: As a prerequisite to use control charts the data have to be normal distributed. Does the PMF holder have to demonstrate that? To identify trends with a control chart about 7 values have to be available. If this number of values is not available due to different reasons a monitoring according to the draft isn’t possible. Proposed change (if any):	**No change** The text has been revised and there is no more mention of upper limits. For monitoring changes graphical tools should be used which are sufficiently indicative to determine any possible trends, but statistical analysis and/or introducing upper limits in control charts are not mandatory for trend analysis. It is not necessary to demonstrate that data are normally distributed. It is not expected that statistical analysis is performed to evaluate trend analysis. If preferred so, upper limits may be added in control charts, but this is not mandatory. This is acceptable for any population/distribution, regardless if it is normally distributed or not. However, if statistical analysis is performed, then statistics using models for normally distributed populations can indeed only be used if normal

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			distribution is demonstrated.
23. Lines 264-269	5	Comment: The level of granularity of the reference level for countries in all cases should be limited. It should be limited to the level of the organization only in cases of exceeding alert limits. Otherwise, the new requirement would increase the workload for PMF Holders without adding any relevant information.	No change proposed.
24. Line 268	1	Comment: "If a country is collecting both whole blood recovered plasma and plasmapheresis plasma it is strongly recommended to monitor changes separately, unless otherwise justified." Proposed change : "If **an organisation** is collecting both whole blood recovered plasma and plasmapheresis plasma, it is strongly recommended to monitor changes separately, unless otherwise justified."	**Rewording has been proposed** *"If both whole blood recovered plasma and plasmapheresis plasma is collected it is strongly recommended to monitor changes separately at country and organisation level, unless otherwise justified."*
25. Lines 267-268	5	Comment: Trend analysis over a long period of time may be misleading due to incomparability of donor recruitment, changes to testing strategies over time [e.g. sensitivity of tests, as well as collection organization changes (merging, opening and/or closure of the centres etc.)] and changes in the donor population over a longer time period. Also, the term "control chart" appropriate; this should be "trend	**No change** Trend analysis over a longer time period is perfectly feasible. If trends/shifts occur due to changes in testing or donor recruitment, then this can be easily justified (and will of course not be regarded as a significant trend). Statistical analyses to determine possible trends are not requested; just graphical presentation seems sufficient and will indicate any obvious

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		analysis with level based on PMF Holder's reference level". Proposed change: Replace "over a period of several years (> 5 years) as far as these data are available" with "over a period of reporting of epidemiological data in the PMF [last calendar year and three (3) previous years], if these data are available". Replace "control chart" with "trend analysis with level based on PMF Holder's reference level should be provided for the last year and three previous years (if these data are available)", as requested for the epidemiological data reporting in the current guideline.	trend. See also comments given for point 12.
26. Lines 270	5	Comment: Upward trends: We suggest to include the comment made by the PPTA at EMA "Plasma master file epidemiology" meeting 18/11/2014 - 19/11/2014: Proposed change (if any): Trend analysis over periods longer than 4 years may be misleading because of potential changes in the donor population (e.g. age) and changes of testing parameters / strategies (e.g. sensitivity of tests); the relevance of retrospective data for the safety of future plasma supply is questionable.	Disagreed. See comments given for point 25. The impact of changes in age or testing strategies over a period of 5 years is most likely irrelevant (or can be clearly stated). On the other hand, trend analysis over a shorter period can be quite misleading, especially in low incidence regions. Trend analysis facilitates the search for reasons in changes of incidence and prevalence. This might well be important also for future products.
27. Lines 272-280	5	Comment: The proposal of using control charts in order to identify upward trends at individual centre level could be useful but the	**see comments for points 16 and 22.**

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		functionality and the contribution of the upper limit calculated from these control charts, as the current draft purposes (e.g. 3xSD), is not sufficiently understood. An upper limit is not a variable for monitoring trends between years but only for identifying outliers in an established donor population. A trend is defined by several points and the positional relation between subsequent pairs of them.	
28. Line 273	5	Comment: Same as for line number 215. Proposed change: Replace ”individual collection centres” with “individual collection centre for source plasma collection centres and processing centres for recovered plasma”.	**see comment for points 9-10-11.**
29. Lines 274-278	5	Comment: Setting up centre-based upper limits deemed unnecessary as centre-based comparison with Alert Levels is performed, identified by PMF Holder and monitored. Centre-based trend analysis is also performed to identify significant upward trends and monitor those centres. These measures are sufficient to monitor the epidemiological data from the donor population donating at the given centre. Given these measures are in place and NAT testing is performed at plasma pool level, setting up the centre-specific upper limits does not provide additional safety assurance.	**see comment for points 16 and 22.**

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		Proposed change: Remove requirement to provide an upper limit calculated on all donations of the respective region collected over several years.	
30. Lines 274-286	2	Comment: Proposed change (if any): Please provide more specific guidance on the setting of alert limits	**No change is proposed** The general guidance provided is considered sufficient.
31. Lines 279-280	5	Comment: The 'Note' in lines 279-280 instructs not to confuse both uppers limits (individual collection centre limit versus alert limit), however, a more detailed clarification would be appreciated. The alert levels already in place (mentioned in the subsequent paragraph) are valid for a comparison with general population, consequently the added value of this new upper level is not clear.	***see comment for point 16.***
32. Lines 284-286	5	Ref. comment - Lines 250-251	**No change proposed** *No acceptance ranges are currently agreed upon. The PMF Holder is expected to propose alert limits of relevance for the specific donor population in the concerned PMF.* *See also comment for point 19*
33. Lines 286-287	5	Comment: For recovered plasma donations both type of donations first time tested (FTT) donors and repeat tested (RT) donors are pooled together. Therefore, setting separate Alert limits for FTT	**No change proposed** *The reasons for the approach taken in the GL are sufficiently addressed in the text (section 9).*

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		and RT donors will not reflect the real situation. Proposed change: To delete the requirement to set separate Alert limits for FTT and RT donors.	*Please note that other parties during the consultation welcomed this approach.*
34. Lines 308 and ff.	5	Comment: "10.1. Window period risk model…" Viraemic portions of window phases for worst case residual risk calculations (HCV 8d, HIV 15d, HBV 35d) should clarify the basic assumptions for their use; i.e. serology and/or NAT testing. In addition, if shorter window periods for viraemic portions of window phases for worst case residual risk calculations are/ have been demonstrated by the PMF Holder due to pool size or due to increased sensitivity of the test(s) used, the PMF Holder should be permitted to apply these.	**Text added "***For reasons outlined above, these worst case window periods are considered appropriate in case of both serology and NAT testing."* **See revised text.**
35. Lines 319-321	5	Comment: As the epidemiological data are calculated as Person-Years, under these conditions (extending the time period to previous years) the comparability of the epidemiological data may be questionable. Proposed change: To delete the requirement "in case no infections in "repeat tested donors" were detected in this year, the time period should be extended to previous years up to and including the	**No change is proposed.** *The approach is considered acceptable as it represents a worst-case calculation.*

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		last year in which an infection was reported".	
36. Lines 324-325	5	Comment: The window period definition should consider not only detection of virus load but also detection of antibodies to viruses (e.g. anti-HCV, anti-HIV-1/-2) for centres which do not perform NAT-testing. Proposed change (in italics): "The window period is a justified estimate of the time period in which a test method is unable to detect an infection in a donation because the viral load or, for centres, where NAT testing is not performed, the antibody concentration is below the methods' limit of detection."	**Proposed wording:** *"The window period is a justified estimate of the time period (length) in which a test method is unable to:* *1) detect a recent infection because there is not yet virus in blood (non-viraemic phase), or* *2) the virus load is below the methods' limit of detection of NAT or antigen testing (viraemic phase), or,* *3) where NAT or antigen testing is not performed, the antibodies are not yet detectable in the testing method applied."*
37. Lines 332-334	5	Comment: The statement "This scenario implies for HIV and HBV less sensitive minipool NATs with only marginal additional benefit when compared to CE-marked antibody (HIV) or HBsAg (HBV) tests" is questionable as in the reality a considerable amount of NAT-only donations can be detected (at least for NSP). Proposed change: To remove this statement.	**Additional wording proposed:** "*This scenario implies for HIV and HBV less sensitive NATs* (e.g. testing of larger minipools as practised by some blood establishments), has only marginal additional benefit when compared to CE-marked antibody (HIV) or HBsAg (HBV) tests.*"*

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38. Lines 336 341	5	Proposed change: "The basic "incidence" method described in this section can (overestimate or underestimate) the…" i.e. the statement should read: The basic "incidence" method described in this section can overestimate or underestimate the… (removal of brackets)	**Proposed wording** *'misestimate (overestimate or underestimate)'*
39. Lines 341-349	12	Comment: A comparison between inter-donation intervals of donors who acquired new infections and inter-donation intervals of all donors is desirable. We would like to note that as the probability of infection is proportional to the length of the donation interval, the mean and median inter-donation intervals of infected donors are expected to be larger than those of the total donor population for any donor population. Also, deviations from the expected distribution of donation intervals of newly infected donors may be caused by various underlying mechanisms, which makes interpretation of such data complex and possibly erroneous. Proposed change (if any): **As deviation from the expected distribution pattern is likely to have only a marginal effect on the risk estimates, it is proposed to remove this section all together.**	**No change is proposed**
40. Lines 345-349	5	Comment: The proposal to report "a) the median interdonation intervals for	***See remark above***

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		their “repeat tested donors” who acquire a new infection” for comparison with “b) the mean interdonation intervals for all “repeat tested donors” should not be required for epidemiological data presentation in the PMF. The infected donors generally tend to delay coming for donating blood due to developing symptoms of infections (for HIV see Schreiber GB et al., 2002) which results in the longer interdonational intervals. Residual risk calculation based on the average interdonation interval of all RT donors will in this case simply overestimate the risk which can be considered then as a ”worst case” estimation. Thus calculation of this ratio does not constitute a safety measure for controlling a residual risk calculation.	
41. Line 350	5	Comment: It should be stated that the “new donor incidence adjustment factor” model is relevant for recovered plasma donors only as source plasma is accepted from RT donors only, as per PPTA standards.	**Not agreed.** *The ‘new donor incidence adjustment factor’ is used to estimate the risk of undetected donations in ‘first time tested donors’, as indicated in section 10.2. In section 11 it is stated that ‘If donations from first time tested donors are used this should be included in the overall estimation of the risk, as well as being presented separately.’ Thus, it is clear from the GL that there is no need to perform calculations for FTT donors if donations are not used. This applies to both source and recovered plasma, as there are also situations where recovered plasma from FTT donors is not used.*
42. Line 357	14,5	Comment: Typo to be corrected.	Accepted

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change: "In scientific literature there are different approaches for determining incidence of infections in “first time tested donors”, mainly for HIV and HCV. However, HBV has similar transmission routes as HIV and H**C**V.”	
43. Line 363	5	Comment: It should be mentioned that the HBV incidence adjustment factor model is relevant for recovered plasma donors only as “for donor populations with an IDI ≤ 77 days the transient nature of HBV infection is not relevant”. The impact of HBV NAT testing should be discussed.	**No change proposed** *The relevance of the HBV incidence adjustment factor depends on the interdonation interval and not on the type of donation (source or recovered).* **Text is revised** The GL already mentions that the presence of detectable amounts of both HBsAg and HBV DNA may be transient. In addition to this, the following is added: ‘As information on the presence of detectable amounts of HBV DNA in HBV infected persons is limited, for the calculation of the ‘window period risk’ it is advised to use a worst-case estimate of the adjustment factor for HBV incidence based on the assumptions used by Korelitz et al.

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44. Line 385	4	Comment: Formula 7: is the formula really changed or just corrected to the 2011 version as the wording is still the same? Proposed change (if any):	**Formula corrected** *The formula is corrected. The term (25% x 0) was left out in the previous version as it equals 0. However, for proper interpretation of the formula it was considered important to include it.*
45. Lines 438-439	5	Comment: "The potential viral load in representative manufacturing pool(s) should be calculated based on the results of the risk estimate(s)." Presenting a calculation based only upon an unrealistic worst case analysis is flawed and not scientifically sound, as it does not truly represent the donor population that ends up in a pool for manufacturing (please see previous general comments' section). The value of such an assessment alone is questionable. The risk calculation should minimally take into account the risk reduction measures for plasma (e.g. inventory hold times for source plasma) to more scientifically assess the risk of the donor population actually entering the manufacturing pool for fractionation (and not be reserved only for the Safety Strategy section). Without considering what donations actually enter the manufacturing pool a worst case analysis is only worse!	**Sentence revised** to indicate that this concerns a worst-case viral load *It is agreed that this is a worst-case situation and risk of an infectious donation entering a plasma-pool may be reduced by other safety measures in place. However, here only the epidemiological data are addressed. The safety measures have no impact on the epidemiology and should therefore not be included in the residual risk/epidemiological data analysis.* *The reason for asking this calculation is to obtain an estimate of the virus load in the manufacturing pool that is associated with the residual risk, as this also is dependent on the pool size and test sensitivities.*

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46. Line 440	4	Comment: Is this new section only valid for new establishments? BE-III (Collection only) is never reported separately for already approved establishments! Proposed change (if any): As it is not possible to report data separately for BE-III delete all requirements for BE-III in section 12.	**Section title revised** The guideline mentions the requirements for approval of new centres and BEs. It may be possible, that in rare cases reporting of epidemiological data is not possible in very small centres. This should be justified.
47. Lines 440-442	4	Comment: different wording for same organizations? Blood establishments versus blood/plasma centre in line 45. See also comment for line 215. Proposed change (if any): Use blood or plasma establishment throughout the whole document.	Text has been harmonised
48. Line 448	4	Comment: 1) Unclear categorizations and not aligned with other regulations. For example: an establishment with no collection but separation, freezing, storage and testing? 2) BE-I: Which category are hospital blood banks as they are not covered by this section? 3) Does BE-I also include processing (separation and freezing) and storage? 4) What category is a BE if testing is outsourced? 5) Is it required to have a BE-I for BE-IIs?	Text has been aligned

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any):	
49. Line 450	5	Comment: 1) “BE-I: Responsibility for all aspects of collection and testing of blood components for all purposes including transfusion”. Is it possible to delegate the testing and stay approved as a BE-I, if the centre guarantees maintenance of chain of custody for the blood components and ensures GMP/ GLP-conform testing? Please clarify. 2) Please also clarify the meaning of “Does not cover hospital blood banks”. Please clarify the rules for hospital blood banks.	See Guideline.
50. Line 453	2	Comment: According to the EMA draft guideline, a BE-III is a blood establishment at which only collection takes place (line 453). The draft guideline states that the data should be reported per country, per organization and per individual collection centre and per calendar year (line 215). Furthermore it is stated that the data should be reported for whole blood donors and plasma donors separately. The PMF-H considers it not desirable to report the epidemiological evaluation per collection centre for the following reasons: 1. All collection centres in the Netherlands are part of one organization, its Blood Bank, operating both a nationwide quality system and a nationwide donor management system. 2. Donor physicians and other personnel are not working in ‘fixed’ teams. They work at various collection centres.	**No changes are proposed** It is acknowledged that different collection systems exist. The Dutch system may be different to systems which are referred to in the guideline. Please refer also to the response to comment 9.

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		3. Geographic (sub)regions do no longer exist since the nationwide systems were implemented. Donors may donate blood or blood components at various collection centres located closely to the place where they live or, for instance, at mobile centres near their work or the place of residence during vacation. A donor can donate whole blood and blood components (by aphaeresis) as well during a calendar year, depending on both his/her preferences and specific requests of the Blood Bank. 4. As the annual number of infected donors per collection centre in the Netherlands is very low (usually 0 or 1), epidemiologic evaluation on this level would be meaningless. 5. This all will result in biased outcomes of epidemiological evaluation if the Dutch data would be reported according to the EMA draft guideline. 6. Collection, logistics and processing of plasma is in the current Dutch model very complex and dynamic, which makes it difficult to report infection numbers on individual collection location. Proposed change (if any): Data from BE III could be merged with the corresponding BE II. If there is a motive (increased donor infection), this PMF-H will evaluate the data on individual centre level.	
51. Lines: 456-461	3	Comment: We do not consider the request to provide 6 months epidemiological data from a significant number of donors is appropriate. Also, it is not clear what 'a significant number' is.	**No change is proposed**

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		Proposed change (if any): 6 months epidemiological data should be submitted, when available, and at the latest with the next annual update.	
52. Lines 456-457 460, 465	5	Comment: A requirement of a minimum amount of epidemiological data for new centres/new organisations would impede the foundation of new centres/organisations, as they would be required to collect plasma for epidemiological data collection without the fractionator being able to use it, which would impact the continuity of plasma supply.	**See response to comment 51**
53. Line 462-466	1	Comment: The requirements for minimum data should be very clear. Proposed change: "A new BE-II or BE-III in a country already included in the concerned PMF could be accepted without submission of epidemiological data, depending on the justification of the PMF older **(e.g. centres located in same regions as centres already included in the PMF and operating in a similar quality system).** However, based on the geographical situation and/or the epidemiological situation of the area where the new BE-II and/or BE-III are located, 6 months epidemiological data may be required. **This may be relevant for large countries ~~such as the USA~~**.	The proposed change ***"(e.g. centres located in same regions as centres already included in the PMF and operating in a similar quality system)."*** Is not acceptable, because too vague. 1) What does it mean with similar quality system? 2) BEs in the same region may not exhibit similar epidemiological data. Proposed deletion of ***"such as the USA"*** is acceptable because it provides only an example.
54. Line 465	4	Comment: Will the 6 months epidemiological data be required by EMA when submitting the PMF?	**No changes proposed**

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): It should be possible to submit a new BE-II without 6 months epidemiological data and deliver the epidemiological data during EMA PMF approval process.	

[i] Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. Official Journal 2003; L33: 30-40.