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Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on draft guideline

Note: This document contains overview of comments received on draft guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008). Column 'Line No of the first line(s) affected' in table 'Specific comments on text' includes references to both the draft and a final version of the guideline.

Interested party (Organisations or individuals) that commented on the draft Guideline as released for consultation

Comments from:

	Name of Organisation or Individual
1.	International Plasma Fractionation Association (IPFA)
2.	Satu Pastila Finnish Red Cross Blood Service
3.	Plasma Protein Therapeutics Association (PPTA)
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1. General comments

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
1	1. This is a highly specialised and technical guideline (even simplified) especially for fractionators who may not own or operate collection centres. Epidemiology is a scientific field mandatory for collectors only and therefore this guideline requires the expertise of epidemiologists who are accustomed to do these calculations. This expertise may not be readily available for some fractionators. 2. Many of the potentially collector-generated data are not available to fractionators and Fractionators have no recognised authority to request such data from collection centres that may therefore have no reason to fell obliged to produce and provide such data. Inspectors do have this authority towards collection centres and it is important that fractionators are not expected to act as collection centre inspectors. Moreover, US centres do not operate under European regulation. 3. The level of information requested by this revision may not improve the quality of plasma-derived medicinal products. Robust measures are indeed in place in the production process in case a donation would be positive for one the viruses and pd-products have proved their complete safety over 15 years. The requirement for epidemiological surveillance will contribute to the safety of blood and blood components but may have little or no impact on quality/safety of pd-Products. This development also highlights the shift of responsibility between fractionators and collectors required by this guideline.	In accordance with Directive 2003/63/EC amending Directive 2001/83/EC, epidemiological data on blood transmissible infections are part of the information required in the PMF. All the effort with the revision of this guideline aims at attaining a harmonised basis for comparing epidemiological data. The scope of the revision has been to provide additional guidance to PMF holders on the: - Submission of epidemiological data - Reporting critical analysis of epidemiological data (e.g. identification and reporting of trends) - residual risk estimations and elements to be considered for the calculations Further to the consultation, the guideline has been revised and clarifications and edits have been put in place across the text aiming for good quality data and reporting.

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
	4. IPFA strongly supports the proposed definitions for first time, repeat and regular donors as these definitions are in line with internationally recognised definitions and provide a scientifically based system for monitoring infectious disease markers in donor populations. However it is important to also recognise that 'applicant donor' systems for plasma collection are capable of delivering suitable and safe plasma for fractionation from donor populations with a relatively higher incidence and prevalence of infectious disease markers.	
	5. The guidance (section 3) has omitted the qualified donor status (maximum inter-donation interval of 6 months) typical of remunerated plasma donors. This is also evident in the recommended methods for converting prevalence to incidence, which is a prerequisite of the incidence-window period model (formula 2 and 3). In qualified donor populations, any confirmed positive test is considered to be a new infection, and therefore the realistic worst case is that prevalence is the same as incidence in these populations. This is a relative disadvantage of this type of plasma, but this is balanced by the contribution to safety provided by look-back, and this is specifically excluded from the risk assessment (section 7.1 paragraph 4). Though it can be addressed in the overall safety strategy.	Guidance is provided in Section 8 on reporting of data where the applicant/qualified donor system is used.
	6. IPFA is concerned that a requirement for presentation of data at 'Centre' level will create problems of definition but also for meaningful statistical and trend analysis in small collection centres. This will be a particular problem for small countries or for blood services operating over large geographical areas with low population densities.	(In general, data should be presented down to the centre level as otherwise relatively high levels at an individual centre may not be detected. Exceptions may be possible on a case-by-case basis where adequately justified (e.g. where centres are very small and the viral marker rates particularly low).)

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
2	The draft includes changes in definitions/formulas, requiring data that is difficult or impossible to obtain from generally used and robust donor registers. Also, there are not-defined formulas included.	Definitions and formulas have been clarified and data should be possible to obtain.
3	Overall, the guideline appears to be very much transfusion oriented and seems to neglect the fact that the PMF is exclusively covering the quality and safety of plasma for fractionation. It should be recognised that Commission Directive 2001/83 defines the scope of the Plasma Master File as “a stand-alone documentation, (…) which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices (…) as regards medical devices incorporating stable derivatives of human blood or human plasma.” With regards to the nature of the plasma for fractionation as the starting material for plasma-derived medicinal products the most important calculation is the estimation of the risk of a potentially infectious unit entering the manufacturing pool, which is not adequately reflected in the proposed revision of the guideline. Specifically, donations that are excluded from manufacture are not relevant and the critical inventory hold is ignored for source plasma. According to the scope the guideline is specifically intended to provide guidance to PMF holders with regards to the collection and reporting of epidemiological data. Therefore, the guideline has to be seen in close conjunction with the PMF as a compilation of all relevant and detailed information on the characteristics of the human plasma used as a starting material for the manufacture of plasma-derived medicinal products. The guideline in its proposed form appears to be more a scientific data	Inventory hold is not ignored but is to be reported and considered at another place of the PMF (Overall safety strategy).

Stakeholder No.	General Comment (if any)	Outcome (if applicable)
	collection of “nice to have” epidemiological data than a guideline relevant to ensuring the quality and safety of pharmaceutical products manufactured from human plasma for fractionation. Therefore, the guideline in its current proposed form will not fulfil its role in the context of licensing such products or enhancing the quality and safety of plasma derived medicinal products. In addition, the proposed new table 3 of the appendices, if intended to be provided per infection/country/organization, will result in a time-consuming exercise regarding the number of documents to be prepared for the PMF.	Table 3 has now been specified for worst case scenarios.

2. Specific comments on text

Line No of the first line(s) affected	Stake-holder No.	Comment and Rationale; proposed changes	Outcome
Page 4 line 37 1. Purpose 5. Recommendations of data on infectious disease markers 6. Epidemiological assessment of donor populations and trends over time	**1**	**Comments:** • Epidemiological data are collected by collection centres and in some countries, are grouped together and analysed by one agency. The analysis is then sent to the fractionator who may not receive the raw data for each donor and from each collection centre. For instance in France, because of the very low incidence in the donor population, each of the regional EFS blood collection centres are currently and should continue to be considered as individual centres (i.e. 15 in total) for the purpose of this guideline. • Also the definition of a centre may encompass small donor 'rooms' that may operate on a part time basis or involve mobile donating centres. Therefore in many cases the data collected will not have a significant number of positive donations to allow for statistically meaningful analysis. Therefore the guidance should be amended in the purpose statement. Following on from the penultimate sentence "Continuous epidemiological...." a condition should be added to allow for situations where small centres may not supply sufficient units in a year to allow for trend analysis. A proposed text is as follows. **Proposed change (if any):** The evaluation and assessment may be more meaningfully performed by combining the results of a group of centres when a number of small collection centres each yield insufficient units to allow for statistically significant analysis of positive rates at the centre level. The choice of the group must be justified and all centres must operate under the same quality system and in the same geographical location.	Not accepted. Case-by-case justification may be possible (see general comment above). Not accepted. Footnote b of the guideline already indicates that the use of the term "collection centre" means a specific site where blood/plasma is collected, including any associated mobile sites.

Page 4, line 53 Section 2 Infectious disease markers	**1**	**Comments:** For some countries like France, anti-HBc is mandatory for blood components but results are not routinely transmitted to LFB. Furthermore, this test is not always considered as highly specific. The guideline should therefore specify the data set of specific disease markers required and exclude those which are designed only as part of a quality/safety system for blood components.	Accepted. AntiHBc has been deleted and a footnote included
.Page 6 lines 38 and page 7 line 5 Section 4	**2**	**Comments:** Discrepancy in text in page 6, paragraph 4, and in Section 5, concerning prevalence in repeat donors. Calculation of incidence (formula 2 and 3): Using the annual number of repeat donors as denominator should be accepted, as obtaining person-years or even the estimate is not possible. **Proposed change (if any):**	Partly accepted. The text has been revised to add clarity, including a statement that the annual number of repeat donors is acceptable as denominator in formula 3.
Page 6 Line 38 Section 4	**1**	**Comments:** • The data required to use formula 2 to calculate incidence will not be available in many cases. Consequently, many applicants will wish to use the alternative method (formula 3) to estimate incidence. This seems to be more a relevant measure of prevalence than incidence. As we understand it, the mean inter-donation interval is calculated as -Number of donors donating in the year divided by the total number of donations donated in the year. If this is a correct interpretation, the total number of donations donated in the year, which appears in both terms in the denominator in formula 3, cancel out, and formula 3 reduces to - No of positive repeat tested donors in the year with a previous negative donation divided by total number of donors. This seems to be a measure of prevalence analogous to formula 1. Whilst this correctly bases the assessment on donors, it fails to take account of a measurement based on	Partly accepted. Text has been revised to add clarity. Formula 3 is calculated on the repeat tested population, the positives are new infections and therefore it is an appropriate approximation of incidence. Conceptually the interdonation interval represents the “period at risk” (ref Schreiber et al 1996). To make this more clear, “at risk” has been added after “person-years” the first time it appears.

		'donations', which is vitally important contribution to the safety of the start pool when using an applicant donor system for remunerated donors. It is of course possible that we have misunderstood how the mean inter-donation interval is to be used, in which case it probably deserves a fuller explanation than that provided in the footnote to formula 3. • We recognize the value of documenting prevalence together with incidence. However, it may not always be possible to calculate incidence in repeat donors in the absence of "the sum of the time between the first and the last test result of every donor during the study period" (formula 2) or "the mean interdonation interval" (formula 3) which are not always available in the data from the collection centres provided to the fractionator. If incidence cannot be calculated, window period risk cannot be calculated and follow up of the risk of infection in the donor population can be done only on the basis of prevalence. In the case of new donors, NAT which is indicative of recent infection can be used to estimate the incidence but it cannot always be applied for HBV when NAT is not done. Furthermore, in this case, antibody only positive first-time donors cannot be included. **Proposed change (if any):**	Positives per number of donations is not a measure of epidemiology. Reference to literature has been included.
Page 6, line 40 formula 2	**4**	**Comments:** In the formula the denominator contains a term "/365". This suggests that the sum of time between the first and the last test results of every donor during the study period is expressed in days, where this is not stated anywhere in the text. If this is indeed the case, division of the denominator by 365 gives the number of person years. At present the term "365" in the formula only puzzles the reader as to what it means rather than that the formula provides a clear definition of incidence. The text after the formula states the desired dimension in which the incidence is preferably expressed. **Proposed change (if any):** Remove "/365 (=person-years)" from formula 2	Accepted. See guidance changes
Page 7, line 24 Section 5 last paragraph	**3**	**Comments:** PPTA strongly objects to the new requirement in section 5 that if within a country both blood banks and plasma source centres are used for the collection of blood/plasma, data for this country should also be summarised separately for each of	Not accepted. The donor population donating whole blood and the donor

		these two categories. Such data reporting is an additional burden with no apparent merit since all plasma comes from certified collection centers and the fractionation process does not handle them separately. In addition, it will add more confusion than clarity, for example in centers collecting both whole blood and plasma, individual donors provide both kinds and blood and plasma donations from these individuals cannot be separated. **Proposed change (if any):** Remove the sentence ~~*"If within a country both blood banks and plasma source centres are used for the collection of blood/plasma, data for this country should also be summarised separately for each of these two categories."*~~	population donating plasma by plasmapheresis can have different epidemiology. Text revised for clarity.
Page 8 line 23 Section 6 Epidemiological assessment of donor populations and trends over time	**1**	The establishment of acceptable ranges should be official and provided by the authorities or collection centres rather than by the fractionator. Industry can neither control or influence population epidemiology but can only *assess* the quality of a centre based on information provided.	Not accepted. PMF holders should use criteria to establish acceptable ranges. Text has been revised for clarity.
Page 9, line 2, last sentence of section 6: "An example"	**4**	**Comments:** The text reads "An example of tests to detect trends has been published" which is incorrect. The paper does not contain a number of tests to detect trends, but one test for trend and one test for outlier detection plus examples of application of both tests for illustration purpose. **Proposed change (if any):** "An example of a test for trend and a test for comparison of centres has been published.[8]"	Accepted. Text revised in the guideline.
Page 9, line 25 Section 7.1, 3rd paragraph	**3**	**Comments:** It is disappointing that parameters such as inventory hold, look-back etc are not taken into account for the risk estimate, although these parameters significantly contribute to the overall safety profile of the plasma pool and thus also to the final product. Again, we would like to stress that the proposed guideline seems to neglect the fact that the PMF describes the quality and safety of human plasma for fractionation, the starting material for plasma-derived medicinal products and rather appears to be geared towards a hypothetical "product" that is not used in any way. The residual risk concept using screening test window periods was originally developed as	

		a method to estimate the risk of receiving a potentially infectious blood unit when being transfused. PPTA has extended the concept to estimate the risk of a potentially infectious unit entering the plasma manufacturing pool, taking into account the critical industry safeguards. As now proposed, the measure is no longer meaningful since it neither measures transfusion risk nor the risk of a potentially infectious plasma unit entering the manufacturing pool since units from first-time test positive donors are not directly used and a major safeguard, the inventory hold, is ignored. The issue of donor quality based on the required reporting of positivity rates is the direct measure that is proposed in the Guidelines to assess centers. **Proposed change (if any):** Residual risk needs to represent a meaningful measure to be useful. Parameters such as inventory hold, look-back, etc should be taken into consideration for the risk estimate of pharmaceutical products manufactured from human plasma for fractionation (where applicable) since that would provide for a more accurate estimate of the residual risk than taking the complete worst case approach.	Not accepted. The intention of this guideline is not to cover *all* safety issues. The introduction to Section 10 states that Section 1.2 of the PMF 'Overall safety strategy' is to appropriate place to consider all parameters. Incidence in first time tested donors is only included in the risk estimation if donations from first time tested donors are used.
Page 9 Line 27	**4**	**Comments:** After the third paragraph a description of a method for calculating the risk of prevalent donors begins. However, the text is still under the section heading "Introduction/general". Only halfway this page the *"Methods"* section begins. **Proposed change (if any):** I would suggest to move the methods header to the third paragraph break on this page, immediately followed with a subsection header "*-Risk from prevalent donors*". The current "*Methods*" header should then be replaced by "*-Risk from new infections in repeat donors*".	Partly accepted. Text has been reorganised for improved clarity.

Page 9 line 37 and page 10 line 8	**2**	**Comments:** Formula 4 is not clear, what does error rate mean, and what is the basis of the formula? Formula 5 is not clear: Page 10, paragraph 2: "risk estimate.. per 100.000 donations. In the previous page, however, formula 5 calculates window period risk using incidence per person years, not per donations. Window-period: mid-point and median value should be defined. **Proposed change (if any):**	Partly accepted. Formula 4 A literature reference is now included. See also comment below from Stakeholder 4. Formula 5 – explanation added of why window period risk is per 100,000 donations. Definitions of mid-point and median value are not considered necessary.
Page 9, line 39 formula 4	**4**	**Comments:** The formula is intended to determine the sum of risk from errors and undetected infections. The last term in this formula reads as a correction term for the summation of independent probabilities. However, the summated terms are not independent as both contain the prevalence! Therefore the quadratic prevalence in the last term is erroneous: it should be linear in prevalence. The first (and third) term in this equation may be multiplied by the positive predictive value of the test (if available) to improve the estimated number of true positive cases. **Proposed change (if any):** Replace formula by: $$\text{Risk} = \left[\frac{1-\text{sensitivity}}{\text{sensitivity}} + \text{error\_rate} - \frac{1-\text{sensitivity}}{\text{sensitivity}} \text{error\_rate} \right] \bullet \text{prevalence}$$	Accepted. Formula amended accordingly.
Page 10, line 24 4th paragraph	**3**	**Comments:** We would respectfully like to point out that the requirement to report the average interdonation intervals for a) “repeat tested donors” who acquire a new infection, and b) all “repeat tested donors” cannot be met. It is impossible to obtain such data as the interdonation intervals (see also comments on appendix, table 3, parameter 3). The introduction of this comparison of interdonation intervals will have little effect on the incidence estimates, which could be lower than calculated by the “incidence” method if	Partly accepted. Sentence now amended to indicate that this information is desirable rather than a requirement.

		infected donors had not delayed their return visits. Donors delaying return would be less likely to be in the screening test window period. **Proposed change (if any):** We strongly recommend deleting this requirement.	
Page 10, line 19 chapter 3,	**2**	**Comments:** Determination of the interdonation interval for all donors, is not possible in practice in our donor register. Estimation of the average interdonation interval should be allowed. **Proposed change (if any):**	Accepted. Text revised taking into account comment.
Page 10 line 29	**2**	**Comments:** "New donor incidence adjustment": should be allowed to use published data on the relative risk of first time donors, if there is no evidence of differing epidemiology in the reporting area. **Proposed change (if any):**	Accepted. Text reworded.
Page 11, line 7 section 7.1, on	**1**	**Comments:** Concerning the HBsAg adjustment factor: it is stated in the second paragraph that the adjustment factor may be taken from the literature (refs. 13-17). We propose that the document prescribes the figure to be used, as this will then be a universally applicable and consistent figure for all parties concerned. **Proposed change (if any):**	A fixed recommendation in the guideline is not relevant (depends for example on donation frequency).
Page 11 line 33 Section 7.2, 3rd bullet:	**1**	**Comments:** The term 'large' is vague and not defined. It is suggested that this term is clarified. **Proposed change (if any):**	Not accepted. Revised guideline now recommends reporting of “worst case” risk assessments and this comment is not relevant to the revised text.
Page 11 line 34 Section 7.2 3rd bullet point	**3**	**Comments:** We strongly question the value of the requirement in section 7.2 to report risk estimates separately for geographical areas etc. It is not common practice to pool plasma for fractionation according to certain regions. Therefore, this information is irrelevant and does not provide any further insight with regards to the safety of the plasma pool. All the more in the light of the fact that – as shown during the EMEA workshop – a center	Accepted. Revised guideline now recommends reporting of “worst case” risk assessments.

		with very high viral marker rates (VMR) may be located in close proximity to a center with very low VMR (Jenkins - Review of geographical spread and trends in plasma donor epidemiological data). Furthermore, this requirement would also raise the question on what basis distinct geographical regions should be defined. In addition, the calculation of residual risk, as we have demonstrated is greatly influenced by factors such as the source inventory hold and donation frequency. We do not believe that any measure that does not encompass these parameters provides a meaningful assessment of risk of a potentially infectious unit entering the manufacturing pool. Risk calculations cannot be easily performed by PMF holders since the level of detail required is not available and the computations are complex, not like for recovered plasma. A data reporting system capable of providing all these data would be extremely cumbersome if not impossible to implement. **Proposed change (if any):** Delete 3rd bullet point	
Page 11 line 42 section 7.3	**1**	**Comments:** This is a very brief instruction and requires further clarification. Presumably there is at least a requirement for 95% confidence intervals around the point estimate **Proposed change (if any):**	Partly accepted. Section 11 now states that the range of uncertainty should be discussed in the dossier.
Page 11 line 44 references	**3**	**Comments:** We would like to propose to remove the reference to Council Recommendation 98/463/EC of 29 June 1998, because this document has been superseded by other documents. Instead, reference should be made to the technical annexes of the Blood Directive or implementing directives. **Proposed change (if any):** Remove reference and replace with reference to the technical annexes of the Blood Directive or implementing directives.	Not accepted. Definitions of donor classification are not included in the directives referred to.
Appendices Page 4 section 3, parameter 3	**3**	**Comments:** As already indicated above, the requirement to report the average (median) interdonation intervals for a) “repeat tested donors” who acquire a new infection, and b) all “repeat tested donors” should be deleted as it is impossible to obtain such data on the interdonation intervals from collection centers. Blood and plasma collection center data systems are not configured to provide such research data. How will these data help assess donor quality?	Partly accepted. Text remains but the use of the ratio is optional, as explained in the corresponding guideline text, as amended.

		Furthermore, the rationale for the calculation of this ratio (mean interdonation versus median interdonation) is unclear. The calculation as requested in Appendix 3 is not in line with the description in Section 7.1 of the proposed guideline. Further clarification would be needed in case this requirement is not removed. For example, an appropriate reference should be provided, if available. **Proposed change (if any):** Delete parameter 3	Accepted, text in the guideline is brought in line with the Appendix.
Page 4, section 3, parameter 4	**3**	**Comments:** We understand that for NAT tested donations, an adjustment factor would not be applicable. The adjustment factor is only justified when donations are solely tested for HBsAg by serology. **Proposed change (if any):** Introduce a footnote: *"The adjustment factor is only justified when donations are solely tested for HBsAg by serology. When donations are tested with NAT an adjustment factor is not applicable."*	Not accepted. The adjustment factor is needed to estimate the *total* number of donors who had a HBV-infection since previous donation, irrespective of the length of NAT-positivity for HBV
Appendix, Table 3:	**2**	**Comments:** Parameter 2: number of donation from repeat donors Parameter 3: mean interdonation interval → estimate of average interdonation interval Parameter 5: window period risk → per 100.000 or 1M donations; new donor incidence estimate, see comment page 10/12 **Proposed change (if any):**	Not accepted (see explanations in the guideline text, as amended).