EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 December 2014

Submission of comments on "Concept paper on revision of Guideline on epidemiological data on blood transmissible infections" (EMA/CHMP/BWP/548524/2008)

Comments from: Plasma Protein Therapeutics Association (PPTA)

Name of organisation or individual

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
26-27		Comment: We understand the purpose is to characterize the donor population with respect to infection risk and allow for comparisons of risks between donor populations and individual centres to ensure donations do not come from donors with high risk of a transmissible blood borne agent. We feel the practice of allowing PMF holders to evaluate their own PMF centres has worked well. The PMF holder should have the responsibility for determining what centres exceed their established limits. It should be noted that even when alert limits might distinguish between an acceptable and a too high risk centre, the centre might exceed the alert limit for one virus but demonstrate completely acceptable incidence rates with regard to the other viruses. That should not automatically lead to the exclusion of this centre from plasma fractionation as high-sensitive NAT pool testing and effective virus reducing manufacturing steps are established resulting in a final product with a high margin of virus safety. Rather this should lead to root cause analysis and initiation of corrective actions to reduce the rates. Proposed change (if any):	
28-29		Comment: As stated the ultimate goal is final product safety. However, the epidemiological assessment in the PMF does not address the product safety. However, the residual risk (RR)	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		assessment with the very low virus loads in the fractionation pool demonstrates that the rates in the donor populations are acceptable. The safety margin based on the established pool testing and virus reduction steps within the manufacturing processes exceeds the calculated RRs by far. Proposed change (if any):	
65-68		Comment: Centre based trending should be covered by risk estimation and internal quality control. Proposed change (if any):	
69-71		Comment: Depending on the epidemiological data set, a conclusive centre-based statistical analysis might be difficult. For example, in a blood collection centre with a low number of donors/donations, rates of 0, 0, 1, 1 positive donations over a period of 4 years strongly affect the trend analysis and the RR estimation. However, such a "doubling" of the incidence can hardly be considered as a significant trend, but it is more related to a so-called “small denominator drive” and statistical variability. Proposed change (if any): Trend analysis is a meaningful tool in addition to the evaluation of alert limits. However, the Guideline should not request the calculation of statistical significances suggesting a scientific precision which is not	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		supported by the amount of data provided by individual collection centres. Assuming that the purpose of the trend analysis is the identification of centres where corrective or preventive actions should be initiated early before these centres might exceed the alert levels, this purpose does not require a complex statistical analysis.	
72-74		Comment: Trend analysis over a long period of time may be misleading due to incomparability of donor recruitment and testing strategies, having changed over time (e.g., sensitivity of tests). Proposed change (if any):	
75-80		Comment: RR calculation is based on epidemiological data provided in Appendix 3 (“raw unmodified” data). RR calculation included the potential for contamination of a plasma pool for fractionation based on the NAT detection limit, NAT window period, virus doubling time, Inventory Hold (for source plasma) and the epidemiological situation in a donor population. In addition, source plasma donors who have not donated in 6 months or more should not be included in the RR calculations since they are prevalent infections and the donor is more similar to the first-time donor. As stated in lines 28-29, the final product safety includes virus reduction capacity by the manufacturing process and should	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		be considered in the RR. Proposed change (if any):	
84-85		Comment: We would support the idea to include additional guidance in the guideline in order to harmonize the different calculation approaches by the different PMF holders. However, with regard to the HBsAg correction factor, its use has to be verified. Today, most of the PMF holders present epidemiological data where donations are tested both serologically and by NAT testing. If the transient nature of the HBsAg results in a false negative testing result in the serological testing, this donation will cause a positive signal in the subsequent NAT testing. Since the sum of both, the serologically positive and the NAT only positive donations, is used for the incidence calculation, there is no need to multiply the number of serologically positive donations with a HBsAg correction factor. However, if this is not acceptable to EMA, the use of a standard correction factor with directions would help guarantee a degree of comparability across PMF submissions. Proposed change (if any): The revised guideline should contain definitions of relevant calculation variables such as the window periods or the new donor incidence adjustment factors to be used. The use of a HBsAg correction factor should be restricted to plasma tested only serologically but not by HBV	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		NAT. Proposed change (if any):	
85-86		Comment: Mathematically, we agree that the epidemiological raw data are strongly affected by the use of multipliers such as the HbsAg correction factor, the new donor incidence correction factors and the applicable window period days. However, a comparison of the RR calculation with shorter (serological + NAT testing) or longer (serological testing only) window periods reveals that the corresponding variability in the final result, i.e. the rate of plasma pools which might be contaminated by 1 window period donation, is irrelevant with regard to the large safety margin achieved by the NAT pool testing and the virus reduction capacity of the manufacturing processes. Company specific approaches should be accepted (use of window periods and NAT is used by each company) if companies can demonstrate shorter window periods with their testing methodologies if there is a standard proposed by EMA. Proposed change (if any):	
87-89		Comment: It does not seem meaningful to extend the observation period in cases where no positive donations were reported by the collection centre. What is the advantage to	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		artificially worsen the actual epidemiological data evaluation by extending the time period in order to include a positive case which was detected 2 years before? This does not provide any conclusions to the actual risk posed by this centre at the time of the PMF application. Reporting incidence rates with different specified time periods will jeopardise comparability of collection centres. Furthermore, this approach is not necessary for plasma for fractionation as a donor population with such a very low incidence (prevalence) rate can be considered acceptable. Proposed change (if any):	
90-95		Comment: A requirement of a minimum amount of epidemiological data for new centres/organisations would impede the foundation of new centres/organisations since they would be required to collect plasma for epidemiological data collection without the fractionator being able to use it. For a newly opened centre there should not be a requirement to provide epidemiology data before inclusion in the PMF. The submitter should evaluate the epidemiology status of a new centre, when possible, to ensure that it complies with their (submitter's) quality requirements. Proposed change (if any):	

Please add more rows if needed.