Plasma Protein Therapeutics Association

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SUBJECT: Follow up on EMEA PMF epidemiology workshop with industry

Dear Dr. Nübling,

Thank you very much for the opportunity to participate in the EMEA PMF epidemiology workshop with industry and to contribute to the discussion on epidemiological data for plasma for fractionation. PPTA participants were generally very positive about the workshop and the discussions we had, but also felt that there may be some points that need further clarification.

Specifically, we would like to highlight the fact that the PPTA *"proposed metric, alert levels for assessing PMF holders source and recovered plasma collection centers for HIV, HCV and HBV"* presented by Dr. George Schreiber, Westat, was based on year 2006 data from collection centers, located in the US and EU, used by PPTA member fractionators, that have been approved in the PMFs as well as through the European inspection system in accordance with the relevant requirements and regulations. The 425 collection centers for source as well as recovered plasma used as the basis for the calculations are approved and routine inspected by EU inspectors for EU-GMP compliance as well as in compliance with Eur. Ph., Directive 2001/83/EC, Directive 2002/98/EC and Directive 2004/33/EC. These centers provide plasma for fractionation as the starting material for the plasma derived products with the currently recognized high level of safety. Thus, we merely reflected this recognized margin of safety in the presented approach to develop the draft viral marker standard and alert levels.

We very much appreciated the presentation of a probabilistic model by Dr. Over. As indicated during the discussion, PPTA is working on the development of a similar model. We believe that a risk based approach provides a suitable tool to gauge any metric used to assess donor quality as well as the impact of other parameters within a more holistic picture of the unique therapies we manufacture. The risk based approach is also supported within the framework of ICH and especially by the European guidelines (e.g. CPMP/BWP/5180/03). While Dr. Over addressed the issue of viral inactivation/removal, his presentation stopped short of providing guidance on acceptable levels in the donor population, which was the focus of the workshop.

Again, we would like to reiterate that there are fundamental differences between labile products intended for transfusion and plasma for fractionation (recovered or source) intended for further manufacture. The estimation of the "risk of missing viraemic donations that may enter the production pool" should therefore take into account risk reduction measures that are implemented, e.g. the inventory hold for source plasma. We believe that the estimation of the residual risk should be based on a realistic picture; otherwise those estimates would provide a completely unrealistic worst case scenario.

Within the holistic frame of the plasma derived products donor selection is only one of the multiple safety measures in place. Measures like inventory hold, NAT testing of donations as well as manufacturing pools, and the virus inactivation/removal steps during the manufacturing process, provide the most important contribution to the overall safety of the plasma derived products. A risk based approach for the development of acceptable ranges for viral markers would also take into account these measures beyond donor selection.

We believe that the complex nature of the assessment and interpretation of epidemiological data needs a continuous exchange of views between all involved parties and we are looking forward to future opportunities for discussion.

Yours sincerely,

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