Plasma Protein Therapeutics Association

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The safety tripod of plasma protein therapies is characterised by the suitability of the donors, the testing of donations, the testing of plasma pools and the pathogen reduction procedures in the manufacturing process. For source plasma, PPTA's voluntary industry standards support these safety measures.

The reduction of the risk that a potentially viraemic donation enters the plasma pool is the result of the contribution of a number of steps starting with criteria for donor selection and the screening of donations, including NAT minipool testing. The epidemiology in the donor population is to be taken into consideration as well as, for instance, the use of donations from first time tested donors for recovered plasma.

The EMEA Guideline on Epidemiological Data on Blood Transmissible Infections requires the reporting of data, the establishment of acceptable ranges or alert levels, including identification of collection centers reporting data above these alert levels and corrective actions taken. The guideline also requires the comparison of data provided over the 3 previous years and the calculation of Residual Risk of missing viraemic donations that may enter the manufacturing pool.

For establishment of alert levels for HBV, HCV and HIV, a harmonized proceeding of all concerned parties is preferable. An approach to establish such levels covering source plasma (SP) as well as recovered plasma (RP), should be applicable for all collection centers in the context of the PMF, based on the following rationale:

- SP and RP are both intended to be used as plasma for fractionation (PFF). Therefore, control measures and testing should be suited for its ultimate use as a raw material.
- SP and RP are collected in the same geographic areas in the US and Europe.
- SP and RP are in some cases even collected in the same collection center.
- Manufacturing pools may contain a mixture of SP and RP.
- The requirements of European Pharmacopoeia monograph on human plasma for fractionation are equivalent for the use of SP and RP.
- The products manufactured from PFF have a wide margin of safety as a result of the multiple safety measures in place, of which the control and monitoring of donors/centers is only one.

Standards for the safety for PFF need to reflect the intended use of this material to manufacture highly purified, pathogen inactivated plasma protein therapies. These standards include testing for pathogens at the donor and manufacturing pool level, which is intended to decrease the presence of viruses of concern to plasma protein therapies. Testing for other pathogens, such as syphilis, West Nile Virus, antibodies to hepatitis B core, and HTLV I, which may be relevant for transfused blood or plasma and are therefore part of the testing of recovered plasma, are not relevant for PFF.

Pertaining to the comparison of data over the previous 3 years we would like to point out that in the case of collection centers with a small donor population a single donation testing reactive by serology or NAT may result in a high positivity rate. In general, on a single collection center level, frequently, very small absolute numbers of positives are observed. Therefore, the statistical probability of a single seroconversion during the observation period might occur by chance, while many centers would have no seroconversions during the same time frame. In conclusion, under these circumstances the statistical evaluation of three years' trending data may not be meaningful.

For the estimation of the Residual Risk the formula as developed by Westat, or an approach similar to it, is used by many companies. It takes into account all relevant parameters while still allowing for flexibility with regards to the use of donations from first time tested donors, the impact of Inventory Hold and NAT testing in a minipool format, including test sensitivity and its effect on the window period. In conclusion, this approach to estimate residual risk is very suitable for the needs of fractionators.

PPTA strongly supports harmonised industry wide procedures for the reporting of data and the definition of Alert Levels. Specifically, for EU licensed collection centers a harmonised approach for data review by national authorities would be desirable and appropriate in view of the provisions of Directive 2002/98/EC, Annex II. As outlined above, appropriate procedures for trending need to be defined as well as a common basis for the estimation of Residual Risk. These agreed approaches and procedures for PMF should be equally embraced and followed by EMEA and national competent authorities.