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A proposed metric, Alert Levels, for assessing PMF holders' source and recovered plasma collection centers for HIV, HCV and HBV, George Schreiber

The manufacture of safe high quality plasma products is based on three components: donor quality, manufacturing pool quality, and viral inactivation and removal steps as part of the fractionation process. A number of factors affect donor risk, such as the population infectious disease risk, donor demographics and donation status (first time/applicant or repeat/qualified). The plasma pool risk is based on donor risk, frequency and volume of donation, sensitivity of serology and NAT testing, and inventory hold (where applicable). Those potential risks can be minimized by appropriate donor screening and laboratory testing. In addition, for source plasma, PPTA has implemented the concept of qualified donors, 60 day inventory hold and viral marker standards. Together, these measures represent a state-of-the-art safety strategy from the donor to the finished product and support confidence in the plasma "margin of safety." . In addition, PPTA for source plasma, has developed measures to evaluate residual risk of a potentially viremic donation entering the manufacturing pool that help monitor quality of the source material.

Infectious disease testing for HIV, HCV and HBV markers during early infection has to take the specific characteristics of the respective virus into account, such as doubling time and length of window period. Risk assessment is an essential tool to ensure plasma quality, patient safety and stakeholder confidence. Risk assessment should be based on epidemiological data and reflect manufacturing practises. Today, there are two key measures, one is the PPTA viral marker standard in place for over a decade. The PPTA standard has proven itself as a statistically reliable system to ensure collection from quality source plasma collection centers, based on viral marker rates. It also serves as a guide for quality improvement. The second measure is described by the EMEA Guideline on Epidemiology Data on Blood Transmissible Infections, requesting to "characterise the donor population with respect to infection risk" and to "allow comparison of risks between donor populations of individual collection centers".

These requirements can be met by the continuous epidemiological evaluation at individual plasma collection centers and implementation of viral marker alert levels, which allow for identification of centers with higher than expected viral positivity rates. Annual update of the assessment including review of the reference rates based on overall industry averages for donors contributing to the pool, measured in a defined time period with the most appropriate testing technology, provide a tool for monitoring "donor quality".

When defining such a standard, two sources of variability in donor center positivity rates have to be taken into account, geographics - demographics and center size (number of donors/donations). Both variables come into play, when considering a metric to assess center "quality".

PPTA has approached this task in two steps. In step one a reference rate of infectious disease marker positivity is determined, by using the overall positivity rate (positive

donors/number of donors) of all the available PPTA member centers reported to EMEA in PMF. In step two the alert levels for a given center are set up, taking into account the variability of the observed positivity rate for a center from the center's expected positivity rate (i.e. Poisson distribution).

PPTA believes that a gamma distribution is appropriate because of the skewed marker rate distribution observed for source and recovered centers and is plausible under a number of assumptions: i) each marker has an overall positivity rate, ii) a center can deviate from this overall positivity rate (i.e. the center's positivity rate has some distribution with mean equal to the overall positivity rate) and iii) the center's observed positivity rate for the year is Poisson distributed with mean equal to the center's positivity rate. With this approach the overall mean positivity rates for HIV, HCV and HBV can be calculated. Based on these figures, from the Gamma distribution virus specific positivity reference rates can be determined. In the next step alert levels are determined by using the Poisson distribution. The number of positives observed should not exceed the normal variation from a Poisson distribution with mean equal to the center reference and the number of donors at the center. The alert levels for HIV, HCV and HBV are calculated by using the EMEA format based on the Poisson distribution at a probability of 0.001 for the 2006 data submitted to EMEA in 2007.

Summary:

Geographic variations in infectious disease prevalence and incidence exist. Therefore, viral removal and inactivation are key to ensuring the safety of fractionated plasma products by removing the risk from a potentially infectious unit that enters the plasma manufacturing pool. Viral inactivation significantly reduces the residual risk in finished plasma products.

PPTA strongly believes that it is feasible to have one standard for both types of plasma, based on the abundance of experience and achievements in the past 15 years. Plasma derived medicinal products have never been safer as a result of the rigorous efforts of the industry to ensure quality donors, sensitive testing, and viral inactivation technologies.

There has been no confirmed case of transmission of viral infection in the last 15 years, attesting to the safety of plasma derived medicinal products.

Outlook – where do we go from here?

As a first step all involved parties need to agree on a common approach to establish Viral Marker Alert/Action levels. These Viral Marker Alert/Action levels should be applicable for all centers independent of plasma type and region. In the future data input for statistical calculations should be extended to include recent data as reported in PMFs (including as many centers as possible).

Ultimately, a "Viral Marker Standard" package should be agreed upon, in which the number of "acceptable" confirmed positive donors (for each viral marker) by center size / number of donors is estimated (based on reference rates as established).

Furthermore, standardized formats for reporting of epidemiological data and standardized timelines for data reporting and responses to follow-up measures are needed as well as a set of 'standardized' follow-up measures, including corrective and preventive actions

(CAPA) by centers exceeding Alert/Action levels to bring those centers back into acceptable range.

A central repository for epidemiological data to facilitate reporting and control of data should be established, to identify centers continuously exceeding action levels, which would be not acceptable to collect plasma for fractionation

In addition, the Qualified Donor Standard for Source Plasma and the established PPTA Viral Marker Standard based on donations from qualified donors will be kept for PPTA member companies as a proven industry quality control measure.