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Calculation of Alert Levels for Assessing Collection Center Donor Quality for PMF Evaluation

Background

The quality and safety of plasma protein therapies and the starting material, human plasma, are critical to ensure the health of the people who use these lifesaving therapies. In order to provide safe plasma protein therapies to patients in need, one measure to be taken is the quality and safety of the starting material, human plasma. The Plasma Protein Therapeutics Association (PPTA) established the International Quality Plasma Program (IQPP¹) in 1997 and Quality Standards of Excellence, Assurance and Leadership (QSEAL²) in 2001 to promote quality practices for the manufacture of plasma protein therapies. The standards within these two programs attend to areas that influence the quality and safety of Source Plasma.

In 2005, the European Medicines Evaluation Agency (EMEA, now European Medicines Agency, EMA) issued its guideline on epidemiological data on blood transmissible infections (London, 20 January 2005, EMEA/CPMP/BWP/125/04) which requires that epidemiological data needs to be submitted as part of the annual PMF-related reports of centers collecting blood and plasma, so-called blood establishments according to Annex II of Directive 2002/98/EC. This requirement is intended to obtain information on the infection risk in specific donor populations and to assess on a regular basis the quality of donors of blood and blood components and plasma for fractionation. The assessment is performed by the competent authorities with the EMA as the coordinating agency. The PMF holder needs to identify acceptable levels (proposed as Alert Levels by the PPTA) for infectious markers. In addition, remedial actions for collection centers that exceed the acceptable level need to be proposed and the effectiveness of the actions taken for centers that have previously been identified as above the acceptable level need to be discussed.

A revised draft of the guideline had been published for public consultation in May 2009 and PPTA Member Companies had provided comments on the draft revision. The final revised guideline has been adopted in May 2010 and is coming into force on 1 January 2011.

The purpose of this document is to propose methods to assess the quality of plasma donor centers using the EMA format.

¹ <http://www.pptaglobal.org/program/iqpp.aspx>

² <http://www.pptaglobal.org/program/qseal.aspx>

1. Data Reporting

Data Reporting

As required by EMA, epidemiological data are collected and compiled on a donor-based approach for each collection center in the PMF. EMA categorizes donors as either first-time tested (FTD) or repeat tested (RTD) and defines positivity rates based on number of donors. The EMA guidelines do not allow for the use of the PPTA IQPP Applicant and Qualified Donor measures in evaluating donor center “quality” for Plasma Master File submissions required for PMF holders. Table 1 gives an overview of the key differences between the definitions for donors in the IQPP and the EMA guidelines. Also indicated are the data elements collected under the new PPTA data system that allows for comparison of the two systems.

Table 1: Key differences between IQPP and the EMA guidelines

		IQPP	EMA	Implication
Donor definition	A ₁	Applicant Donors	FTD	Compared to Qualified Donors, RTD show an increased number of positives (numerator) by adding A ₂ and A _r positive cases which are Applicant Donors according to IQPP
	A ₂		RTD	
	A _r			
	Q	Qualified Donors		
Rate calculation	Numerator	Positives	Positives	Decrease the denominator by calculation on a per donor basis, thus increase rates
	Denominator	# donations	# donors	

A₁ = 1st applicant donation

A₂ = 2nd applicant donation

A_r = previously qualified donor returning with > 6 month lapse

It has to be highlighted that the data reported in each fractionator’s PMF are in compliance with the EMA definition of first-time tested and repeat tested donor. Therefore the above table and the following section serve just as a cross-reference to enable the Companies to contrast differences in the values for positive markers from the two systems: IQPP and EMA.

1.1 Comparison of reporting formats

Due to the different donor classifications and rate calculations, the virus positivity rates for plasma for fractionation will be changed by employing the EMA format, compared to the positivity rates based on Qualified Donors. This is a result of using the repeat tested definition, rather than using the Qualified Donor definition. As illustrated in Table 1, both donors making the second Applicant Donation and Qualified Donors who have not donated in 6 months or longer are considered repeat donors by EMA.

The above mentioned differences in the definitions are important to note when trying to compare positivity rates or any other numbers calculated from them that are based on different underlying definitions, because data collected and reported according to the PPTA IQPP format (Applicant & Qualified Donors) may not be compared to the data collected and reported according to the EMA required format (first-time & repeat tested donors). However, both reporting systems for donor quality control serve to help ensure the safety of plasma protein therapeutics.

Since FTD source plasma is not used until the donor has been qualified by two non-reactive screening tests on subsequent samples, the safety of plasma products can be ensured even if the then qualified donor donates in centers with higher viral marker positivity rates.

1.2 Interpretation of donor quality under EMA guideline

1.2.1 Methods to assess donor quality according to EMA guideline

a. Donor classifications

First-time tested donor (FTD)

Donor whose blood/plasma is tested for the first-time for infectious disease markers (with or without donation) without evidence of prior testing in a given blood system.

Repeat tested donor (RTD)

Donor whose blood/plasma has been tested previously for infectious disease markers in a given blood system.

b. Viral markers and testing

Confirmed infection of human immunodeficiency virus (**HIV**), hepatitis B virus (**HBV**) and hepatitis C virus (**HCV**) are defined as:

Confirmed seropositive

Repeatedly reactive (= 2 times reactive) in a screening test and positive in at least one supplementary test based on a different principle.

NAT only positive

Positive in a NAT assay for a specific virus (HIV, HCV or HBV), not found seropositive for that virus in serological screening, and shown to be true positive by separate NAT or later serology.

c. Positivity Rates

The primary metric assessing epidemiological data used by EMA based on donors is the positivity rate of HIV, HCV and HBV for FTD and RTD based on donors in each category (refer to EMA 'GUIDELINE ON EPIDEMIOLOGICAL DATA' appendix table 1 and 2 for FTD and RTD):

$$\text{Positivity Rate} = \frac{\text{confirmed seropositive} + \text{NAT only positive}}{\text{No of donors tested in a given calendar year}} \quad (1)$$

1.3 Interpretation of “donor quality” under EMA guideline

Applying the EMA guidelines to calculate viral marker positivity rates using formula (1) for plasma collection centers will generate data as shown in Table 2 for each center. PMF holders can use these listings to assess the virus rates at each of their collection sites.

Table 2: Viral marker positivity rates per 10⁵ donors using the EMA format

	N_{FTD}	N_{FTD+}	N_{RTD}	N_{RTD+}	FTD rates	RTD rates
HIV						
HBV						
HCV						

For so-called recovered plasma (i.e. plasma derived from whole blood donations) donations from both FTD and RTD are used in the manufacturing pool. For source plasma (i.e. plasma obtained by plasmapheresis for the purpose of further manufacture into plasma protein therapies; source plasma as collected by PPTA member companies follows the IQPP standard) donations from FTD only are not used. Therefore, for donors of recovered plasma the measure employed should take into account the contribution of both first-time and repeat tested donors to the plasma collected and a composite positivity rate as a measure of the overall center donor quality should be applied. It is important to note that whole blood (recovered plasma) establishments vary considerably in the percentage of new donors and those establishments with a larger regular donor base will have fewer positive donors since it is recognized that repeat donors have significantly lower positivity rates.

Therefore, we use a weighted composite rate (which can be calculated by blood centers or PMF holders/fractionators) as a measure of overall donor quality for recovered plasma:

$$R_{FTD+RTD} = (R_{FTD} \times \frac{N_{FTD}}{N_{FTD} + N_{RTD}}) + (R_{RTD} \times \frac{N_{RTD}}{N_{FTD} + N_{RTD}}) = \frac{N_{FTD+} + N_{RTD+}}{N_{FTD} + N_{RTD}};$$

This composite rate represents the total number of positive donors/the total number of all donors where

- R_{FTD} = FTD positivity rate
- R_{RTD} = RTD positivity rate
- N_{FTD} = number of first-time tested donors
- N_{RTD} = number of repeat tested donors
- N_{FTD+} = number of positive FTD
- N_{RTD+} = number of positive RTD.

2. Donor Center Quality Metrics

To develop a donor center quality metric, each of the PPTA Member Companies submitted their data reported to EMA in the 2008 Plasma Master Files to Westat, the company that serves as the independent data coordinating center for PPTA. The data in the format required by EMA were processed and analyzed by Westat. The data reported by each company was entered into a database.

Since a collection site may appear in PMFs of more than one fractionator, comparisons of center information were performed to identify suppliers that provided plasma to more than one company to avoid duplication of data. Also, as a measure for data quality, the data reported for collection sites appearing on multiple PMFs were compared.

The final data set contained one record for each unique plasma collection center (source or recovered plasma). There were 34 recovered plasma centers and 139 source plasma centers that were either reported by multiple fractionators or required clarification due to incomplete data.

As shown in Table 3 there were 300 unique recovered plasma centers and 375 unique source plasma centers reported on the seven PMFs of the PPTA member PMF holders. Most of the recovered plasma centers were European based (94%). For source plasma centers 27% were located in Europe with the remainder located in the U.S.

Table 3: Number of Recovered and Source Plasma Collection Centers in PMFs of PPTA Member PMF holders, 2008

	RECOVERED			SOURCE			Total
	EUROPE	USA	All	EUROPE	USA	All	
# of centers	281	19	300	102	273	375	675

Table 4 shows the number of blood and plasma collection establishments (recovered and source) as well as the country of origin of each of the plasma collection centers. About 56% of the recovered plasma centers were located in Germany and Sweden. Of the 102 European centers collecting source plasma, 73% were located in Germany. It has to be kept in mind that blood establishments are usually more heterogeneous ranging from small hospital collection sites to regional collection establishments like for example the Red Cross in Bavaria.

Table 4: Number of Recovered and Source Plasma Collection Centers in PPTA Member companies PMFs, by country, 2008

Countries	# of centers		
	Recovered	Source	Total
AUSTRIA	10	18	28
BELGIUM	2	0	2
CZECH REPUBLIC	39	9	48
DENMARK	11	0	11
FINLAND	3	0	3
GERMANY	82	74	156
LUXEMBURG	1	0	1
POLAND	20	0	20
SWEDEN	85	1	86

Countries	# of centers		
	Recovered	Source	Total
SWITZERLAND	28	0	28
USA	19	273	292
Total	300	375	675

With regards to the total number of donors, Table 5 shows the numbers of both first-time and repeat-tested donors. As may be expected, the majority were at blood establishments providing recovered plasma (83%). As also shown in Table 5, 83% of donors providing recovered plasma were repeat donors while 68% of the source plasma donors were classified as repeat tested.

Table 5: Number of Recovered and Source Plasma Donors in 2008 in PPTA Member companies PMFs

		# of donors	
		RECOVERED	SOURCE
TOTAL FT DONOR	Total	1,403,130	626,119
TOTAL RPT DONOR	Total	5,386,618	1,302,058
TOTAL FT+RPT DONORS	Total	6,512,856	1,928,177

Due to the fact that a center may supply plasma to multiple PMF holders and the issue of differences in the reporting of results by the plasma collection centers, data quality controls need to be incorporated into the data processing and analyses to guarantee accuracy of the information. When calculating overall donor rates this is especially important since whole blood (i.e. recovered plasma) establishments have a greater number of donors, which can significantly affect the denominators.

Risk assessment is recognized as an important tool to ensure plasma quality and safety and – ultimately – patient safety. The EMA guideline on Epidemiological Data on Blood Transmissible Infections calls for donor based measures to “*characterize the donor population with respect to infection risk, and allow comparison of risks between donor populations of individual collection centers.*” Plasma used for fractionation in Europe is derived from a large number of collection centers located in a number of countries throughout Europe as well as in the U.S.A. It is well known that substantial geographical and demographic variations exist in infectious diseases. Thus, considerable variations in donor positivity rates are also expected, especially for first-time donors who represent primarily prevalent cases of infection. In considering a metric for assessing the quality of donor centers the geographic and demographic variation in disease incidence come into play. The use of a standard measure to assess viral marker rates will allow fractionators to identify collection centers with viral positivity rates higher than normally expected, and further to investigate the centers, and take corrective measures where necessary.

First-time donors are recognized to have higher infectious disease rates than repeat donors; largely due to these being prevalent infections. Plasma from first-time tested donors only is used for fractionation only if recovered from whole blood. As for source plasma, PPTA Member Companies

use only units obtained from repeat tested donors (i.e. plasma from first-time tested donors is not used for fractionation). This exclusive use of source plasma from repeat tested donors together with the inventory hold period greatly reduces the risk of window period donations entering the manufacturing pool.

In establishing a quality control metric for evaluating donor centers it is desirable to have one measure that applies to both types of plasma for fractionation – recovered and source plasma. Therefore, the Alert Level quality assurance measure (defining acceptable ranges for epidemiological data) as proposed in this document can be used to assess donor populations at both recovered and source collection centers on the level of individual centers.

As stated in the EMA Guideline, the goal is to allow for identification of blood and plasma establishments with higher than expected viral positivity rates and to also allow for the continuous monitoring of individual centers. From the quality control standpoint, identification of outliers is important to help maintain center quality and to allow for analysis of deviations.

To that end a two step process for establishing Alert Levels has been developed. The first step is to determine a reference rate of donor infectious disease positivity based on results reported to EMA in the PMFs. The second step is then to establish the maximum number of acceptable positives that would not be expected to exceed normal variation from the Poisson distribution using the reference level of positivity and center number of donors.

The following features are part of the donor center Alert Levels:

- Establishes specific single cut-off levels for each viral marker.
- Allows for uniform application to all plasma collection centers – independent of the type of plasma collected and/or the size of the center.
- Simplifies the data reporting by PMF holders while also allowing easy interpretation by regulators.
- Serves as a guide for quality improvement.
- Allows continuous monitoring of epidemiological data.
- Allows the identification of outlier centers, i.e. centers that exceed the Alert Level so that investigative and remedial actions may be initiated where appropriate.
- Establishes reference rates, measured in a defined time period, based on industry data and representing the overall donor positivity rate for centers supplying source and recovered plasma to fractionators.
- Allows for periodic assessment of reference rates and Alert Levels.

3. Statistical Methodology

3.1 Statistical Background

The goal of the evaluation of the epidemiological data is to establish a metric to be used to assess donor quality of plasma collection centers. This metric should be applicable to assess donor centers that collect source and recovered plasma since both are used in the manufacturing process for plasma protein therapies. Plasma used for manufacturing plasma-derived medicinal products to be distributed in Europe comes from centers that have considerable geographic and demographic diversity. The prevalence rates of the population for the three viruses relevant for evaluating donor quality also vary due to these factors. In addition, the actual numbers of positive donors at each center are generally very small; thus there will be considerable statistical variance in the number of

positives from time period to time period that, when coupled with the variation in the number of collections, produces positivity rates that will by statistical chance alone be expected to vary. When the distributions of positivity rates for any of the viruses are examined they are skewed to the right with some degree of apparent outliers. To account for these factors it is desirable to develop a metric that takes into account the prevalence in the population, natural variance in positivity rates, as well as the size of the collection center. The measure to be employed should identify outliers that are unlikely to be chance occurrences.

Comparison of the crude positivity rates does not allow for an appropriate evaluation since it does not take into consideration the statistical variance. The aim is to maintain donor quality by identifying centers that have higher than expected rates so that the cause of the higher rate may be investigated and corrective interventions initiated as appropriate. In this section we describe the statistical background for the metric we developed that will serve as a quality control measure for donor centers.

It is very common to describe a given numerical dataset using the mean and standard deviation. However, these parameters are most useful as descriptors only under the assumption of normality or approximate normality of the distribution of the underlying data at hand. These descriptors (i.e. mean and standard deviation) should be used cautiously and may be very misleading if the underlying distribution is far from normal; for example, if the distribution is highly skewed, asymmetric or the data may take only a limited set of values. It should be also noted that, it is statistically correct to use the mean and standard deviation of a dataset to infer control limits (e.g. 99% upper control limit based on mean + 3 SD) only under the assumption of normality. Therefore, this approach of describing the data by mean and standard deviation is not applicable to the positivity rates for HIV, HBV and HCV. In fact, in these cases simple descriptive statistics show strong deviations from normality for each of the viral markers (detectable by specific statistical tests, such as the Anderson-Darling). For these datasets it is typical that the positivity rates are low at most centers but there are a few centers which have a high positivity rate. Thus, the underlying distribution of center specific positivity rates is highly asymmetric, usually with a high peak at the lower end of the scale, near zero, and a long right tail – this is very far from the bell shaped normal distribution, where the vast number is concentrated around the center of the distribution, with symmetric tails on either side.

In non-normal situations, empirical techniques may be used to fit different distributions to the observed data to find the best match. Using such techniques, it was found that the best fit was a Gamma distribution, which approximated the observed distribution shape. The Gamma distribution can be characterized by two descriptive parameters, the scale parameter θ and shape parameter κ . (In terms of the formulation given below, $\kappa=1/\phi$ and $\theta=\phi\mu$). In this situation, Alert Levels for positivity rates will be dependent on the specific parameters for the Gamma distribution used.

It should be noted however, that this Gamma distribution of center specific positivity rates is unobserved. What is observed, however, is the number of donors that come to the centers and how many of those donors test positive. Thus, the Alert Level will need to be in terms of observed numbers of positive donors. Hence, a discrete distribution to describe the actual data obtained is needed. For ease of understanding, the discrete distribution of the number of positive donors that is observed at any center is first described, giving the center specific positivity rate. This is assumed to be a Poisson distribution with the underlying unobserved center specific positivity rate as its parameter.

Combining the postulated Gamma and Poisson distributions yields the distribution of the data actually observed, which is calculated as a Negative Binomial distribution, with its parameters depending on the descriptors of the theoretical Gamma and the Poisson distributions. Thus, to fit the

observed data one must carry out a negative binomial regression as described below. Finally, this combination of the two distributions, Poisson and Gamma, allows the definition of Alert Levels in a consistent statistical scenario.

3.2 Negative Binomial Regression

For plasma data, for any given disease such as HIV, HCV, HBV etc, it is first assumed that each collection center has its own unique underlying center-specific positivity rate with no center having a rate of zero. This underlying center-specific positivity rate is not observed. Let the i th center have positivity rate μ_i . We assume that, conditional on this rate, the observed count Y_i of positive cases of the specific disease follows a Poisson distribution with mean μ_i . at center i . Symbolically,

$$Y_i|\mu_i \sim \text{Poisson}(\mu_i)$$

We then assume that the unobserved positivity rates μ_i follow a Gamma distribution with mean μ , which describes the average underlying positivity rate over all the centers and dispersion parameter, which describes the variation in positivity rates among the different centers. Symbolically, this assumption can be expressed as

$$\mu_i \sim \text{Gamma}(\text{mean} = \mu \text{ variance} = \phi\mu^2)$$

Under these conditions, from this two step process, the unconditional distribution of Y_i is a negative binomial with mean μ and variance $\mu + \phi\mu^2$. Symbolically,

$$Y_i \sim \text{Negative Binomial}(\mu, \mu + \phi\mu^2)$$

Thus, we apply a negative binomial regression to the annual plasma center data (Y_i , $i=1,2,\dots,K$) where K is the total number of plasma collection centers.

3.3 Alert Levels

It is also required to set Alert Levels to identify centers where the positivity rate is unacceptably high. As in many statistical process control scenarios the Alert Level (or upper control limit) is set to identify only extreme outliers (to prevent ‘overreaction’ due to the large number of centers to be evaluated). The suggested alpha level is thus 0.005.

For a center i , let Y_i be the number of positive donors out of n total donors. The center sample positivity rate should not exceed the typical variation from a negative binomial distribution with mean μ and variance $\mu + \phi\mu^2$. We derive a cut-off point κ (i.e. Alert Level) by using this negative binomial distribution such that

$$P(Y_i \geq \kappa | \mu, \phi) = 0.005$$

This can be done in two steps. First, the 99.5th percentile for the center specific positivity rate is estimated assuming a Gamma distribution with mean μ , and dispersion parameter ϕ . Let this be termed μ_{ref} , the center reference limit. Let Y_i be the number of positive donors out of n total donors, then derive a cut-off point κ (i.e. Alert Level) by using a Poisson distribution with mean $n\mu_{ref}$, as

$$P(Y_i \geq \kappa | n\mu_{ref}) = 0.005$$

3.4 Estimation

There are six plasma center datasets; datasets for source and recovered centers, and datasets for HIV, HBV, and HCV. One possibility would be to run six individual regressions. However, the datasets have been analyzed in a single regression. First, different ‘Alert Levels’ for source and recovered plasma centers were deemed undesirable. Second, a common dispersion parameter for the three

markers was found to be adequate. The dispersion parameter was therefore calculated on the total positivity rate which was the sum of all positives for the three viruses. The negative binomial regression then estimated three marker specific mean positivity rates and one common dispersion parameter.

The Alert Levels of a marker for a center can then be determined from the estimated marker mean positivity rate, the estimated common dispersion parameter, and the number of donors at the center.

The overall mean positivity rates for the three viral markers in 2008 were (see **Table 6**) 5.07 (HIV), 23.58 (HBV), and 34.64 (HCV). The estimated dispersion parameter is 1.82, estimated using all marker data from both source and recovered centers. The 99.5th percentile for the center specific positivity rate is estimated assuming a Gamma distribution and assuming a common dispersion parameter for all markers. Since 7.5 is the 99.5th percentile from the normalized Gamma, with dispersion 1.82, a center specific positivity rate should not exceed 7.5 times the overall mean rate. This is the center reference limit. Figure 1 shows the Gamma distribution with a dispersion factor of 1.82 and the 99.5% center positivity rate.

Figure 1: Presumed distribution of positivity rates among centers, where the overall positivity rate is λ .

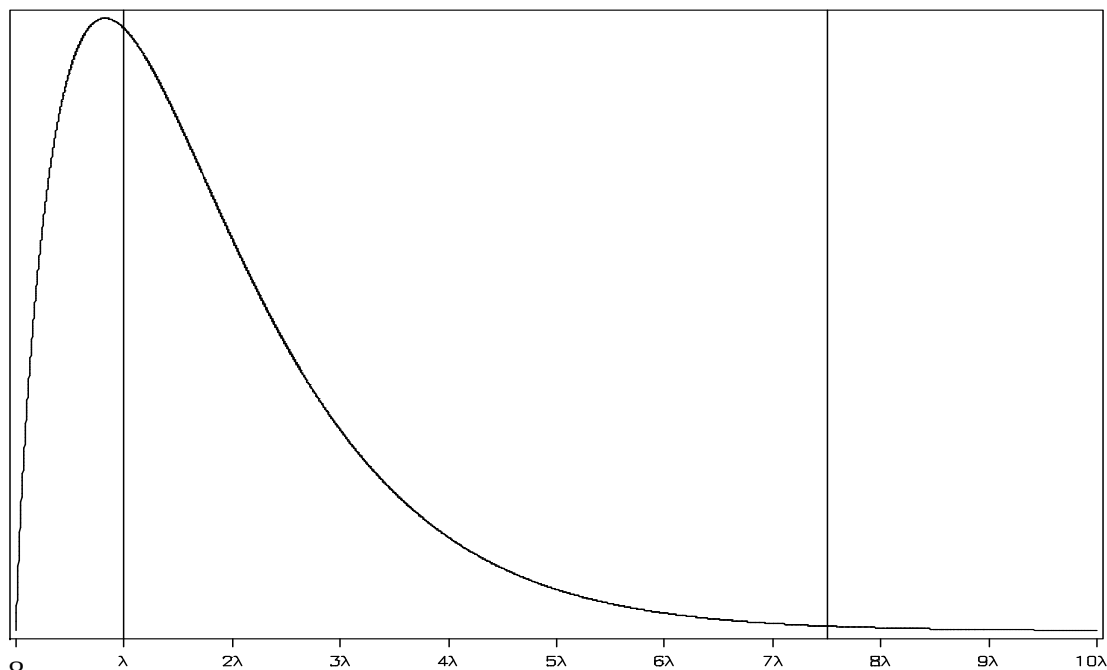


Figure 1 shows a Gamma distribution with dispersion parameter equal to 1.82 (as estimated in the negative binomial regression). Most centers will have a positivity rate near λ (vertical reference line at λ), however many centers will have lower rates, and a few centers will have rates several times larger.

The 99.5th percentile for the Gamma is 7.5 times the mean (vertical reference line at 7.5λ), meaning a center's positivity rate should only rarely exceed 7.5 times the overall mean marker positivity rate.

The respective reference rates per 100,000 donors for the three viral markers are then 37.77 (HIV), 175.67 (HBV), and 258.07 (HCV).

The number of positives should not exceed normal variation from a Poisson distribution with mean equal to the center reference limit times the center number of donors. The application of the Poisson distribution to determine the allowable number of positive donors given the center's number of donors follows.

The Alert Levels will be set based on PMF data for 2008 and data of subsequent years will be measured against the rates defined here. The rates and corresponding Alert Levels will be reviewed periodically. Rates would not be adjusted up unless there were recognized regional or global population shifts in positivity rates observed. Likewise, if drops in donor positivity rates for any virus are consistently documented the reference rates could be adjusted downward to increase the effectiveness of the quality metric.

Table 6: PPTA Member PMF holders Positivity Rates from Centers in PMFs, distributional parameters, and reference rates, 2008

Number of Centers	Recovered	300
	Source	375
	All	675
Overall Positivity Rate (per 100,000 Donors)	HIV	5.07
	HBV	23.58
	HCV	34.64
Gamma Dispersion Factor		1.82
Gamma Reference (99.5%)		7.5
Reference rate*	HIV	37.77
	HBV	175.67
	HCV	258.07

*Reference rate = Overall positivity rate x Gamma Reference.

In calculating the positivity rates for all recovered plasma centers first-time donors were included, except where donations from first-time donors are not allowed to be used for transfusion or plasma collection by national regulations. In the cases of these centers they were thus treated similar to source centers where first-time donors are not incorporated in the calculation of positivity rates.

4. Viral marker Alert Levels based on Poisson distribution

This section for setting quality assurance limits is designed to be applicable to both source and recovered plasma collection centers and relies on centralized collection and processing of PPTA Member Companies collection center data to define Alert Levels for HIV, HBV and HCV.

The viral marker Alert Levels are based on Poisson distribution probability tables. These tables assess the relative probability of any number of confirmed positive donors based on any given number of total donors and a combined reference value for viral positive rates for source plasma repeat tested donors, and all recovered plasma donors. For PPTA member PMF holders the reference value for each of the three specified viruses is derived from data from all collection sites submitted in the PMFs to EMA using 2008 as the reference year (2008 has been chosen as the most

"up to date information" on positivity rates³). Determination of the reference levels is detailed in the statistical section above. Thus, each plasma collection center can be assessed regularly within a given timeframe (i.e. calendar year according to EMA guidelines) based on its own donor population. The use of probabilities as an assessment tool permits fair comparisons of all plasma centers regardless of the number of total collections for a given period.

For identifying collection centers with higher than expected viral marker rates it is proposed to use the same method as the PPTA viral marker Alert Limits system (IQPP Viral Marker Standard). The Alert Levels are set at a probability of 0.001 for the individual viral markers. This means that a plasma center would exceed the Alert Level if it had more positive donors than would be expected 99.9% of the time for a plasma center based on their number of donors for a given period. The actual number of positive donors that would put a plasma center at a level exceeding the Alert Level will depend on two factors: (1) the number of donors at a plasma center for a given period and (2) the reference rate. The reference rate refers to the overall plasma collection site viral marker rates that serve as the basis for establishing the probability tables. Based on the parameters indicated above, lookup tables have been produced that enable the collection centers and/or PMF holders to easily assess whether a center exceeded the Alert Level. These lookup tables are developed based on number of donors at the center. By finding the row for the number of donors that donated at the given establishment in the table the number of positive donors that are allowed before the Alert Level is exceeded can easily and readily be determined. Thus, PMF holders' collection centers have a swift way of gauging their donor quality. The respective lookup tables for each of the three viral markers are indicated in Appendix 1 starting on page 14.

These reference rates may be adjusted periodically. An adjustment might be necessary in case the number and/or the composition of collection centers that contribute plasma for fractionation to the PPTA member companies' PMFs change significantly. As proposed above, however, the data for 2008 will serve as the reference and no upward adjustments would be made to the rates unless there was ample documented evidence of population based shifts in infectious disease rates for any of the three viruses, HIV, HCV and HBV.

Details of setting up Alert Levels using Poisson distribution

- using the reference positivity rate to estimate the expected cases μ for any size of donor population at a given center: $\mu = \text{positivity rate} \times \text{\#donors}$
- estimating cut-off point k by using any given μ and cumulative probability $p(x \leq k) = 0.999$ or $p(x > k) = 0.001$ (where x is # of positive cases)

All centers supplying plasma for fractionation have already gone through the regulatory review process as well as the necessary inspections by an EU competent authority and have received the respective approvals. The collection centers located in the U.S., in addition, have received the necessary FDA approvals. These centers are thus recognized as suppliers of plasma with an appropriate safety margin. Thus, the choice of the probability rate for the Alert Levels recognizes this fact.

The objective of this donor center quality assurance measure is to detect high outliers. For those centers that exceed the Alert Levels (i.e. the outliers) specific actions can be initiated like root cause analyses and corrective and preventive actions. The objective of having one unified system of Alert Levels for plasma for fractionation is also to ensure that new plasma collection centers are within

³ The reference values have been verified to be consistent with those estimated based on 2006 and 2007 data.

acceptable levels of donor quality. Periodic evaluations of the reference rates will be performed under the umbrella of PPTA for their Member Companies.

Using the calculated reference rates, Alert Level tables have been developed for each viral marker by center size as determined by the number of donors. Given that for source plasma PPTA Member Companies use only donations from repeat tested donors, in this case for the metric the number of donors will be reflecting the repeat-tested donors⁴ only as required by EMA, while for recovered plasma the number will be the total donors at the center, since plasma from both – first-time and repeat-tested donors – is used. These 'look-up tables' allow both PMF holders and plasma suppliers (as the organizations responsible for the individual centers) to assess the quality of their centers easily and quickly. Rates for the first-time tested and repeat tested donors will be reported to EMA as required.

Centers that exceed the Alert Levels have immediate impact in triggering actions as listed in the “*Corrective and Preventive Action Points to Consider to Address Centers Exceeding Alert Levels*” (EPITF100xx). In 2008, 3 centers triggered such corrective and preventive action points.

An underlying assumption on using positivity rates to assess center quality is that there is a relationship between the detection of donors who present with positive viral markers and the quality of the manufacturing pool. It is important to emphasize that all positive or questionable donations are removed from further processing and thus will never enter the manufacturing process. If a donor center exceeds an Alert Level for a viral marker it does not mean it is automatically ineligible to supply plasma for fractionation in the future. Further acceptability of a center that exceeded an Alert Level will depend on the effectiveness of any actions initiated as a follow-up, as well as the possibility that the outlier high rate might be a chance occurrence. Possible steps to investigate the elevated rate are presented in EPITF10014 (7 September 2010).

In summary, the approach presented in this document provides a tool to evaluate the quality of an individual plasma collection center based on the epidemiological data reported in a given timeframe. The system of Alert Levels in look up tables based on center size allows an easy and feasible quality control measure to identify outliers for both the PMF holders and the plasma collection organizations. It also provides a tool for PMF holders to evaluate potential new collection sites based on their individual positivity rates for the viral markers in a given timeframe.

Appendix 1: Lookup tables for HCV, HBV & HIV

Viral marker Alert Levels for HCV

(based on 2008 positivity data for FTD & RTD (recovered plasma) and for RTD (source plasma) as reported in PMFs; with $p = 258/100000$ and a limit of 0.001)

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
1	17	1
18	73	2
74	166	3
167	286	4
287	429	5
430	589	6
590	763	7
764	950	8
951	1147	9
1148	1353	10
1354	1566	11
1567	1787	12
1788	2013	13
2014	2245	14
2246	2482	15
2483	2724	16
2725	2969	17
2970	3219	18
3220	3472	19
3473	3728	20
3729	3987	21
3988	4249	22
4250	4514	23
4515	4781	24
4782	5051	25
5052	5323	26
5324	5597	27
5598	5873	28
5874	6150	29
6151	6430	30
6431	6711	31
6712	6994	32
6995	7279	33
7280	7565	34

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
7566	7852	35
7853	8141	36
8142	8431	37
8432	8722	38
8723	9015	39
9016	9309	40
9310	9604	41
9605	9900	42
9901	10197	43
10198	10495	44
10496	10794	45
10795	11094	46
11095	11395	47
11396	11696	48
11697	11999	49
12000	12303	50
12304	12607	51
12608	12912	52
12913	13218	53
13219	13525	54
13526	13832	55
13833	14140	56
14141	14449	57
14450	14758	58
14759	15068	59
15069	15379	60
15380	15690	61
15691	16002	62
16003	16315	63
16316	16628	64
16629	16942	65
16943	17256	66
17257	17571	67
17572	17886	68

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
17887	18202	69
18203	18519	70
18520	18835	71
18836	19153	72
19154	19471	73
19472	19789	74
19790	20108	75
20109	20427	76
20428	20747	77
20748	21067	78
21068	21387	79
21388	21708	80
21709	22029	81
22030	22351	82
22352	22673	83
22674	22996	84
22997	23319	85
23320	23642	86
23643	23966	87
23967	24290	88
24291	24614	89
24615	24939	90
24940	25264	91
25265	25589	92
25590	25915	93
25916	26241	94
26242	26567	95
26568	26894	96
26895	27221	97
27222	27548	98
27549	27876	99
27877	28204	100
28205	28532	101
28533	28861	102

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
28862	29189	103
29190	29518	104
29519	29848	105
29849	30177	106
30178	30507	107
30508	30837	108
30838	31168	109
31169	31499	110
31500	31830	111
31831	32161	112
32162	32492	113
32493	32824	114
32825	33156	115
33157	33488	116
33489	33820	117
33821	34153	118
34154	34486	119
34487	34819	120
34820	35152	121
35153	35486	122
35487	35819	123
35820	36153	124
36154	36488	125
36489	36822	126
36823	37157	127
37158	37491	128
37492	37826	129
37827	38162	130
38163	38497	131
38498	38833	132
38834	39168	133
39169	39504	134
39505	39841	135
39842	40177	136
40178	40514	137
40515	40850	138
40851	41187	139
41188	41524	140
41525	41862	141

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
41863	42199	142
42200	42537	143
42538	42874	144
42875	43212	145
43213	43551	146
43552	43889	147
43890	44227	148
44228	44566	149
44567	44905	150
44906	45244	151
45245	45583	152
45584	45922	153
45923	46262	154
46263	46601	155
46602	46941	156
46942	47281	157
47282	47621	158
47622	47961	159
47962	48302	160
48303	48642	161
48643	48983	162
48984	49324	163
49325	49664	164
49665	50005	165
50006	50347	166
50348	50688	167
50689	51030	168
51031	51371	169
51372	51713	170
51714	52055	171
52056	52397	172
52398	52739	173
52740	53081	174
53082	53424	175
53425	53766	176
53767	54109	177
54110	54452	178
54453	54795	179
54796	55138	180

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
55139	55481	181
55482	55824	182
55825	56168	183
56169	56511	184
56512	56855	185
56856	57198	186
57199	57542	187
57543	57886	188
57887	58230	189
58231	58575	190
58576	58919	191
58920	59263	192
59264	59608	193
59609	59953	194
59954	60297	195
60298	60642	196
60643	60987	197
60988	61333	198
61334	61678	199
61679	62023	200
62024	62368	201
62369	62714	202
62715	63060	203
63061	63405	204
63406	63751	205
63752	64097	206
64098	64443	207
64444	64789	208
64790	65136	209
65137	65482	210
65483	65828	211
65829	66175	212
66176	66521	213
66522	66868	214
66869	67215	215
67216	67562	216
67563	67909	217
67910	68256	218
68257	68603	219

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
68604	68951	220
68952	69298	221
69299	69645	222
69646	69993	223
69994	70341	224
70342	70688	225
70689	71036	226
71037	71384	227
71385	71732	228
71733	72080	229
72081	72428	230
72429	72777	231
72778	73125	232
73126	73473	233
73474	73822	234
73823	74170	235
74171	74519	236
74520	74868	237
74869	75217	238
75218	75566	239
75567	75915	240
75916	76264	241
76265	76613	242
76614	76962	243
76963	77311	244
77312	77661	245
77662	78010	246
78011	78360	247
78361	78709	248
78710	79059	249
79060	79409	250
79410	79759	251
79760	80109	252
80110	80459	253
80460	80809	254
80810	81159	255
81160	81509	256
81510	81859	257
81860	82210	258

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
82211	82560	259
82561	82911	260
82912	83261	261
83262	83612	262
83613	83962	263
83963	84313	264
84314	84664	265
84665	85015	266
85016	85366	267
85367	85717	268
85718	86068	269
86069	86419	270
86420	86771	271
86772	87122	272
87123	87473	273
87474	87825	274
87826	88176	275
88177	88528	276
88529	88880	277
88881	89231	278
89232	89583	279
89584	89935	280
89936	90287	281
90288	90639	282
90640	90991	283
90992	91343	284
91344	91695	285
91696	92047	286
92048	92400	287
92401	92752	288
92753	93104	289
93105	93457	290
93458	93809	291
93810	94162	292
94163	94515	293
94516	94867	294
94868	95220	295
95221	95573	296
95574	95926	297

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
95927	96279	298
96280	96632	299
96633	96985	300
96986	97338	301
97339	97691	302
97692	98044	303
98045	98398	304
98399	98751	305
98752	99104	306
99105	99458	307
99459	99811	308
99812	100165	309
100166	100519	310
100520	100872	311
100873	101226	312
101227	101580	313
101581	101934	314
101935	102288	315
102289	102641	316
102642	102995	317
102996	103349	318
103350	103704	319
103705	104058	320
104059	104412	321
104413	104766	322
104767	105121	323
105122	105475	324
105476	105829	325
105830	106184	326
106185	106538	327
106539	106893	328
106894	107247	329
107248	107602	330
107603	107957	331
107958	108312	332
108313	108666	333
108667	109021	334
109022	109376	335
109377	109731	336

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
109732	110086	337
110087	110441	338
110442	110796	339
110797	111151	340
111152	111507	341
111508	111862	342
111863	112217	343
112218	112573	344
112574	112928	345
112929	113283	346
113284	113639	347
113640	113994	348
113995	114350	349
114351	114706	350
114707	115061	351
115062	115417	352
115418	115773	353
115774	116128	354
116129	116484	355
116485	116840	356
116841	117196	357
117197	117552	358
117553	117908	359
117909	118264	360
118265	118620	361
118621	118976	362
118977	119333	363
119334	119689	364
119690	120045	365
120046	120401	366
120402	120758	367
120759	121114	368
121115	121471	369
121472	121827	370
121828	122184	371
122185	122540	372
122541	122897	373
122898	123254	374
123255	123610	375

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
123611	123967	376
123968	124324	377
124325	124681	378
124682	125037	379
125038	125394	380
125395	125751	381
125752	126108	382
126109	126465	383
126466	126822	384
126823	127179	385
127180	127537	386
127538	127894	387
127895	128251	388
128252	128608	389
128609	128966	390
128967	129323	391
129324	129680	392
129681	130038	393
130039	130395	394
130396	130753	395
130754	131110	396
131111	131468	397
131469	131825	398
131826	132183	399
132184	132541	400
132542	132898	401
132899	133256	402
133257	133614	403
133615	133972	404
133973	134330	405
134331	134687	406
134688	135045	407
135046	135403	408
135404	135761	409
135762	136119	410
136120	136477	411
136478	136836	412
136837	137194	413
137195	137552	414

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
137553	137910	415
137911	138268	416
138269	138627	417
138628	138985	418
138986	139343	419
139344	139702	420
139703	140060	421
140061	140419	422
140420	140777	423
140778	141136	424
141137	141494	425
141495	141853	426
141854	142212	427
142213	142570	428
142571	142929	429
142930	143288	430
143289	143646	431
143647	144005	432
144006	144364	433
144365	144723	434
144724	145082	435
145083	145441	436
145442	145800	437
145801	146159	438
146160	146518	439
146519	146877	440
146878	147236	441
147237	147595	442
147596	147954	443
147955	148313	444
148314	148673	445
148674	149032	446
149033	149391	447
149392	149751	448
149752	150110	449
150111	150469	450
150470	150829	451
150830	151188	452
151189	151548	453

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
151549	151907	454
151908	152267	455
152268	152626	456
152627	152986	457
152987	153346	458
153347	153705	459
153706	154065	460
154066	154425	461
154426	154784	462
154785	155144	463
155145	155504	464
155505	155864	465
155865	156224	466
156225	156584	467
156585	156944	468
156945	157303	469
157304	157663	470
157664	158023	471
158024	158384	472
158385	158744	473
158745	159104	474
159105	159464	475
159465	159824	476
159825	160184	477
160185	160544	478
160545	160905	479
160906	161265	480
161266	161625	481
161626	161986	482
161987	162346	483
162347	162706	484
162707	163067	485
163068	163427	486
163428	163788	487
163789	164148	488
164149	164509	489
164510	164869	490
164870	165230	491
165231	165591	492

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
165592	165951	493
165952	166312	494
166313	166673	495
166674	167033	496
167034	167394	497
167395	167755	498
167756	168116	499
168117	168476	500
168477	168837	501
168838	169198	502
169199	169559	503
169560	169920	504
169921	170281	505
170282	170642	506
170643	171003	507
171004	171364	508
171365	171725	509
171726	172086	510
172087	172447	511
172448	172808	512
172809	173170	513
173171	173531	514
173532	173892	515
173893	174253	516
174254	174615	517
174616	174976	518
174977	175337	519
175338	175699	520
175700	176060	521
176061	176421	522
176422	176783	523
176784	177144	524
177145	177506	525
177507	177867	526
177868	178229	527
178230	178590	528
178591	178952	529
178953	179313	530
179314	179675	531

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
179676	180037	532
180038	180398	533
180399	180760	534
180761	181122	535
181123	181484	536
181485	181845	537
181846	182207	538
182208	182569	539
182570	182931	540
182932	183293	541
183294	183655	542
183656	184016	543
184017	184378	544
184379	184740	545
184741	185102	546
185103	185464	547
185465	185826	548
185827	186188	549
186189	186550	550
186551	186913	551
186914	187275	552
187276	187637	553
187638	187999	554
188000	188361	555
188362	188723	556
188724	189086	557
189087	189448	558
189449	189810	559
189811	190173	560
190174	190535	561
190536	190897	562
190898	191260	563
191261	191622	564
191623	191984	565
191985	192347	566
192348	192709	567
192710	193072	568
193073	193434	569
193435	193797	570

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
193798	194159	571
194160	194522	572
194523	194884	573
194885	195247	574
195248	195610	575
195611	195972	576
195973	196335	577
196336	196698	578
196699	197061	579
197062	197423	580
197424	197786	581
197787	198149	582
198150	198512	583
198513	198874	584
198875	199237	585
199238	199600	586
199601	199963	587
199964	200326	588
200327	200689	589
200690	201052	590
201053	201415	591
201416	201778	592
201779	202141	593
202142	202504	594
202505	202867	595
202868	203230	596
203231	203593	597
203594	203956	598
203957	204319	599
204320	204683	600
204684	205046	601
205047	205409	602
205410	205772	603
205773	206135	604
206136	206499	605
206500	206862	606
206863	207225	607
207226	207589	608
207590	207952	609

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
207953	208315	610
208316	208679	611
208680	209042	612
209043	209405	613
209406	209769	614
209770	210132	615
210133	210496	616
210497	210859	617
210860	211223	618
211224	211586	619
211587	211950	620
211951	212314	621
212315	212677	622
212678	213041	623
213042	213404	624
213405	213768	625
213769	214132	626
214133	214495	627
214496	214859	628
214860	215223	629
215224	215587	630
215588	215950	631
215951	216314	632
216315	216678	633
216679	217042	634
217043	217406	635
217407	217769	636
217770	218133	637
218134	218497	638
218498	218861	639
218862	219225	640
219226	219589	641
219590	219953	642
219954	220317	643
220318	220681	644
220682	221045	645
221046	221409	646
221410	221773	647
221774	222137	648

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
222138	222501	649
222502	222866	650
222867	223230	651
223231	223594	652
223595	223958	653
223959	224322	654
224323	224686	655
224687	225051	656
225052	225415	657
225416	225779	658
225780	226143	659
226144	226508	660
226509	226872	661
226873	227236	662
227237	227601	663
227602	227965	664
227966	228329	665
228330	228694	666
228695	229058	667
229059	229423	668
229424	229787	669
229788	230152	670
230153	230516	671
230517	230881	672
230882	231245	673
231246	231610	674
231611	231974	675
231975	232339	676
232340	232703	677
232704	233068	678
233069	233433	679
233434	233797	680
233798	234162	681
234163	234527	682
234528	234891	683
234892	235256	684
235257	235621	685
235622	235985	686
235986	236350	687

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
236351	236715	688
236716	237080	689
237081	237445	690
237446	237809	691
237810	238174	692
238175	238539	693
238540	238904	694
238905	239269	695
239270	239634	696
239635	239999	697
240000	240364	698
240365	240729	699
240730	241094	700
241095	241459	701
241460	241824	702
241825	242189	703
242190	242554	704
242555	242919	705
242920	243284	706
243285	243649	707
243650	244014	708
244015	244379	709
244380	244744	710
244745	245109	711
245110	245475	712
245476	245840	713
245841	246205	714
246206	246570	715
246571	246935	716
246936	247301	717
247302	247666	718
247667	248031	719
248032	248396	720
248397	248762	721
248763	249127	722
249128	249492	723
249493	249858	724
249859	250223	725
250224	250588	726

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
250589	250954	727
250955	251319	728
251320	251685	729
251686	252050	730
252051	252416	731
252417	252781	732
252782	253147	733
253148	253512	734
253513	253878	735
253879	254243	736
254244	254609	737
254610	254974	738
254975	255340	739
255341	255705	740
255706	256071	741
256072	256437	742
256438	256802	743
256803	257168	744
257169	257534	745
257535	257899	746
257900	258265	747
258266	258631	748
258632	258996	749
258997	259362	750
259363	259728	751
259729	260094	752
260095	260459	753
260460	260825	754
260826	261191	755
261192	261557	756
261558	261923	757
261924	262288	758
262289	262654	759
262655	263020	760
263021	263386	761
263387	263752	762
263753	264118	763
264119	264484	764
264485	264850	765

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
264851	265216	766
265217	265582	767
265583	265948	768
265949	266314	769
266315	266680	770
266681	267046	771
267047	267412	772
267413	267778	773
267779	268144	774
268145	268510	775
268511	268876	776
268877	269242	777
269243	269609	778
269610	269975	779
269976	270341	780
270342	270707	781
270708	271073	782
271074	271439	783
271440	271806	784
271807	272172	785
272173	272538	786
272539	272904	787
272905	273271	788
273272	273637	789
273638	274003	790
274004	274370	791
274371	274736	792
274737	275102	793
275103	275469	794
275470	275835	795
275836	276201	796
276202	276568	797
276569	276934	798
276935	277301	799
277302	277667	800
277668	278033	801
278034	278400	802
278401	278766	803
278767	279133	804

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
279134	279499	805
279500	279866	806
279867	280232	807
280233	280599	808
280600	280965	809
280966	281332	810
281333	281699	811
281700	282065	812
282066	282432	813
282433	282798	814
282799	283165	815
283166	283532	816
283533	283898	817
283899	284265	818
284266	284632	819
284633	284998	820
284999	285365	821
285366	285732	822
285733	286098	823
286099	286465	824
286466	286832	825
286833	287199	826
287200	287566	827
287567	287932	828
287933	288299	829
288300	288666	830
288667	289033	831
289034	289400	832
289401	289766	833

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
289767	290133	834
290134	290500	835
290501	290867	836
290868	291234	837
291235	291601	838
291602	291968	839
291969	292335	840
292336	292702	841
292703	293069	842
293070	293436	843
293437	293803	844
293804	294170	845
294171	294537	846
294538	294904	847
294905	295271	848
295272	295638	849
295639	296005	850
296006	296372	851
296373	296739	852
296740	297106	853
297107	297473	854
297474	297840	855
297841	298208	856
298209	298575	857
298576	298942	858
298943	299309	859
299310	299676	860
299677	300043	861
300044	300411	862

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
300412	300778	863
300779	301145	864
301146	301512	865
301513	301880	866
301881	302247	867
302248	302614	868
302615	302981	869
302982	303349	870
303350	303716	871
303717	304083	872
304084	304451	873
304452	304818	874
304819	305185	875
305186	305553	876
305554	305920	877
305921	306287	878
306288	306655	879
306656	307022	880
307023	307390	881
307391	307757	882
307758	308125	883
308126	308492	884
308493	308860	885
308861	309227	886
309228	309595	887
309596	309962	888
309963	310000	889

Viral marker Alert Levels for HIV

(based on 2008 positivity data for FTD & RTD (recovered plasma) and for RTD (source plasma) as reported in PMFs; with $p = 38/100000$ and limit of 0.001)

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
1	2	0
3	119	1
120	501	2
502	1127	3
1128	1945	4
1946	2913	5
2914	4000	6
4001	5186	7
5187	6453	8
6454	7790	9
7791	9188	10
9189	10638	11
10639	12134	12
12135	13672	13
13673	15247	14
15248	16856	15
16857	18495	16
18496	20163	17
20164	21856	18
21857	23574	19
23575	25313	20
25314	27074	21
27075	28853	22
28854	30651	23
30652	32465	24
32466	34296	25
34297	36141	26
36142	38001	27
38002	39874	28
39875	41760	29
41761	43659	30
43660	45569	31
45570	47490	32
47491	49421	33
49422	51363	34
51364	53315	35
53316	55275	36

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
55276	57245	37
57246	59223	38
59224	61210	39
61211	63204	40
63205	65207	41
65208	67216	42
67217	69233	43
69234	71256	44
71257	73287	45
73288	75323	46
75324	77366	47
77367	79416	48
79417	81470	49
81471	83531	50
83532	85597	51
85598	87669	52
87670	89746	53
89747	91828	54
91829	93915	55
93916	96006	56
96007	98103	57
98104	100203	58
100204	102309	59
102310	104419	60
104420	106533	61
106534	108651	62
108652	110773	63
110774	112899	64
112900	115029	65
115030	117163	66
117164	119300	67
119301	121441	68
121442	123586	69
123587	125734	70
125735	127885	71
127886	130040	72
130041	132198	73

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
132199	134359	74
134360	136523	75
136524	138691	76
138692	140861	77
140862	143034	78
143035	145210	79
145211	147389	80
147390	149571	81
149572	151756	82
151757	153943	83
153944	156133	84
156134	158325	85
158326	160520	86
160521	162717	87
162718	164917	88
164918	167119	89
167120	169324	90
169325	171531	91
171532	173740	92
173741	175952	93
175953	178165	94
178166	180381	95
180382	182599	96
182600	184820	97
184821	187042	98
187043	189266	99
189267	191493	100
191494	193721	101
193722	195951	102
195952	198184	103
198185	200418	104
200419	202654	105
202655	204892	106
204893	207132	107
207133	209373	108
209374	211617	109
211618	213862	110

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
213863	216109	111
216110	218357	112
218358	220607	113
220608	222859	114
222860	225113	115
225114	227368	116
227369	229625	117
229626	231883	118
231884	234143	119
234144	236405	120
236406	238668	121
238669	240932	122
240933	243198	123
243199	245465	124
245466	247734	125

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
247735	250005	126
250006	252276	127
252277	254550	128
254551	256824	129
256825	259100	130
259101	261377	131
261378	263656	132
263657	265936	133
265937	268217	134
268218	270499	135
270500	272783	136
272784	275068	137
275069	277355	138
277356	279642	139
279643	281931	140

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
281932	284221	141
284222	286512	142
286513	288805	143
288806	291098	144
291099	293393	145
293394	295689	146
295690	297986	147
297987	300284	148
300285	302583	149
302584	304883	150
304884	307185	151
307186	309487	152
309488	310000	153

Viral marker Alert Levels for HBV

(based on 2008 positivity data for FTD & RTD (recovered plasma) and for RTD (source plasma) as reported in PMFs; with $p = 176/100000$ and a limit of 0.001)

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
1	25	1
26	108	2
109	243	3
244	420	4
421	629	5
630	863	6
864	1119	7
1120	1393	8
1394	1682	9
1683	1983	10
1984	2296	11
2297	2619	12
2620	2951	13
2952	3292	14
3293	3639	15
3640	3993	16
3994	4353	17
4354	4719	18
4720	5089	19
5090	5465	20
5466	5845	21
5846	6229	22
6230	6617	23
6618	7009	24
7010	7404	25
7405	7803	26
7804	8204	27
8205	8609	28
8610	9016	29
9017	9426	30
9427	9838	31
9839	10253	32
10254	10670	33
10671	11089	34
11090	11511	35
11512	11934	36

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
11935	12359	37
12360	12786	38
12787	13215	39
13216	13646	40
13647	14078	41
14079	14512	42
14513	14948	43
14949	15385	44
15386	15823	45
15824	16263	46
16264	16704	47
16705	17146	48
17147	17590	49
17591	18035	50
18036	18481	51
18482	18928	52
18929	19377	53
19378	19826	54
19827	20277	55
20278	20728	56
20729	21181	57
21182	21634	58
21635	22089	59
22090	22545	60
22546	23001	61
23002	23458	62
23459	23916	63
23917	24376	64
24377	24835	65
24836	25296	66
25297	25758	67
25759	26220	68
26221	26683	69
26684	27147	70
27148	27611	71
27612	28076	72

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
28077	28542	73
28543	29009	74
29010	29476	75
29477	29944	76
29945	30413	77
30414	30882	78
30883	31352	79
31353	31822	80
31823	32293	81
32294	32765	82
32766	33237	83
33238	33710	84
33711	34183	85
34184	34657	86
34658	35132	87
35133	35607	88
35608	36082	89
36083	36558	90
36559	37035	91
37036	37512	92
37513	37989	93
37990	38467	94
38468	38946	95
38947	39424	96
39425	39904	97
39905	40384	98
40385	40864	99
40865	41345	100
41346	41826	101
41827	42307	102
42308	42789	103
42790	43272	104
43273	43754	105
43755	44238	106
44239	44721	107
44722	45205	108

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
45206	45690	109
45691	46174	110
46175	46659	111
46660	47145	112
47146	47631	113
47632	48117	114
48118	48604	115
48605	49090	116
49091	49578	117
49579	50065	118
50066	50553	119
50554	51041	120
51042	51530	121
51531	52019	122
52020	52508	123
52509	52998	124
52999	53488	125
53489	53978	126
53979	54468	127
54469	54959	128
54960	55450	129
55451	55942	130
55943	56433	131
56434	56925	132
56926	57418	133
57419	57910	134
57911	58403	135
58404	58896	136
58897	59389	137
59390	59883	138
59884	60377	139
60378	60871	140
60872	61365	141
61366	61860	142
61861	62355	143
62356	62850	144
62851	63346	145
63347	63841	146
63842	64337	147

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
64338	64834	148
64835	65330	149
65331	65827	150
65828	66324	151
66325	66821	152
66822	67318	153
67319	67816	154
67817	68314	155
68315	68812	156
68813	69310	157
69311	69808	158
69809	70307	159
70308	70806	160
70807	71305	161
71306	71804	162
71805	72304	163
72305	72804	164
72805	73304	165
73305	73804	166
73805	74304	167
74305	74805	168
74806	75306	169
75307	75807	170
75808	76308	171
76309	76809	172
76810	77311	173
77312	77813	174
77814	78315	175
78316	78817	176
78818	79319	177
79320	79821	178
79822	80324	179
80325	80827	180
80828	81330	181
81331	81833	182
81834	82337	183
82338	82840	184
82841	83344	185
83345	83848	186

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
83849	84352	187
84353	84856	188
84857	85361	189
85362	85865	190
85866	86370	191
86371	86875	192
86876	87380	193
87381	87885	194
87886	88391	195
88392	88896	196
88897	89402	197
89403	89908	198
89909	90414	199
90415	90920	200
90921	91427	201
91428	91933	202
91934	92440	203
92441	92947	204
92948	93454	205
93455	93961	206
93962	94468	207
94469	94975	208
94976	95483	209
95484	95991	210
95992	96499	211
96500	97007	212
97008	97515	213
97516	98023	214
98024	98531	215
98532	99040	216
99041	99549	217
99550	100057	218
100058	100566	219
100567	101075	220
101076	101585	221
101586	102094	222
102095	102603	223
102604	103113	224
103114	103623	225

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
103624	104133	226
104134	104643	227
104644	105153	228
105154	105663	229
105664	106173	230
106174	106684	231
106685	107195	232
107196	107705	233
107706	108216	234
108217	108727	235
108728	109238	236
109239	109750	237
109751	110261	238
110262	110772	239
110773	111284	240
111285	111796	241
111797	112308	242
112309	112819	243
112820	113332	244
113333	113844	245
113845	114356	246
114357	114868	247
114869	115381	248
115382	115894	249
115895	116406	250
116407	116919	251
116920	117432	252
117433	117945	253
117946	118458	254
118459	118972	255
118973	119485	256
119486	119998	257
119999	120512	258
120513	121026	259
121027	121540	260
121541	122053	261

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
122054	122567	262
122568	123082	263
123083	123596	264
123597	124110	265
124111	124625	266
124626	125139	267
125140	125654	268
125655	126168	269
126169	126683	270
126684	127198	271
127199	127713	272
127714	128228	273
128229	128743	274
128744	129259	275
129260	129774	276
129775	130290	277
130291	130805	278
130806	131321	279
131322	131837	280
131838	132353	281
132354	132869	282
132870	133385	283
133386	133901	284
133902	134417	285
134418	134933	286
134934	135450	287
135451	135966	288
135967	136483	289
136484	137000	290
137001	137516	291
137517	138033	292
138034	138550	293
138551	139067	294
139068	139584	295
139585	140102	296
140103	140619	297
140620	141136	298
141137	141654	299
141655	142171	300

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
142172	142689	301
142690	143207	302
143208	143724	303
143725	144242	304
144243	144760	305
144761	145278	306
145279	145796	307
145797	146315	308
146316	146833	309
146834	147351	310
147352	147870	311
147871	148388	312
148389	148907	313
148908	149426	314
149427	149944	315
149945	150463	316
150464	150982	317
150983	151501	318
151502	152020	319
152021	152539	320
152540	153059	321
153060	153578	322
153579	154097	323
154098	154617	324
154618	155136	325
155137	155656	326
155657	156176	327
156177	156695	328
156696	157215	329
157216	157735	330
157736	158255	331
158256	158775	332
158776	159295	333
159296	159815	334
159816	160336	335
160337	160856	336
160857	161376	337
161377	161897	338
161898	162418	339

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
162419	162938	340
162939	163459	341
163460	163980	342
163981	164500	343
164501	165021	344
165022	165542	345
165543	166063	346
166064	166584	347
166585	167106	348
167107	167627	349
167628	168148	350
168149	168669	351
168670	169191	352
169192	169712	353
169713	170234	354
170235	170756	355
170757	171277	356
171278	171799	357
171800	172321	358
172322	172843	359
172844	173365	360
173366	173887	361
173888	174409	362
174410	174931	363
174932	175453	364
175454	175975	365
175976	176498	366
176499	177020	367
177021	177543	368
177544	178065	369
178066	178588	370
178589	179110	371
179111	179633	372
179634	180156	373
180157	180679	374
180680	181202	375
181203	181725	376
181726	182248	377
182249	182771	378

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
182772	183294	379
183295	183817	380
183818	184340	381
184341	184863	382
184864	185387	383
185388	185910	384
185911	186434	385
186435	186957	386
186958	187481	387
187482	188004	388
188005	188528	389
188529	189052	390
189053	189576	391
189577	190100	392
190101	190624	393
190625	191148	394
191149	191672	395
191673	192196	396
192197	192720	397
192721	193244	398
193245	193768	399
193769	194293	400
194294	194817	401
194818	195342	402
195343	195866	403
195867	196391	404
196392	196915	405
196916	197440	406
197441	197964	407
197965	198489	408
198490	199014	409
199015	199539	410
199540	200064	411
200065	200589	412
200590	201114	413
201115	201639	414
201640	202164	415
202165	202689	416
202690	203214	417

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
203215	203740	418
203741	204265	419
204266	204790	420
204791	205316	421
205317	205841	422
205842	206367	423
206368	206892	424
206893	207418	425
207419	207944	426
207945	208469	427
208470	208995	428
208996	209521	429
209522	210047	430
210048	210573	431
210574	211099	432
211100	211625	433
211626	212151	434
212152	212677	435
212678	213203	436
213204	213729	437
213730	214256	438
214257	214782	439
214783	215308	440
215309	215835	441
215836	216361	442
216362	216888	443
216889	217414	444
217415	217941	445
217942	218468	446
218469	218994	447
218995	219521	448
219522	220048	449
220049	220575	450
220576	221101	451
221102	221628	452
221629	222155	453
222156	222682	454
222683	223209	455
223210	223736	456

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
223737	224264	457
224265	224791	458
224792	225318	459
225319	225845	460
225846	226373	461
226374	226900	462
226901	227427	463
227428	227955	464
227956	228482	465
228483	229010	466
229011	229538	467
229539	230065	468
230066	230593	469
230594	231121	470
231122	231648	471
231649	232176	472
232177	232704	473
232705	233232	474
233233	233760	475
233761	234288	476
234289	234816	477
234817	235344	478
235345	235872	479
235873	236400	480
236401	236928	481
236929	237456	482
237457	237985	483
237986	238513	484
238514	239041	485
239042	239570	486
239571	240098	487
240099	240627	488
240628	241155	489
241156	241684	490
241685	242212	491
242213	242741	492
242742	243270	493
243271	243798	494
243799	244327	495

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
244328	244856	496
244857	245385	497
245386	245914	498
245915	246442	499
246443	246971	500
246972	247500	501
247501	248029	502
248030	248558	503
248559	249088	504
249089	249617	505
249618	250146	506
250147	250675	507
250676	251204	508
251205	251734	509
251735	252263	510
252264	252792	511
252793	253322	512
253323	253851	513
253852	254381	514
254382	254910	515
254911	255440	516
255441	255969	517
255970	256499	518
256500	257029	519
257030	257558	520
257559	258088	521
258089	258618	522
258619	259148	523
259149	259678	524
259679	260207	525
260208	260737	526
260738	261267	527
261268	261797	528
261798	262327	529
262328	262857	530
262858	263388	531
263389	263918	532
263919	264448	533
264449	264978	534

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
264979	265508	535
265509	266039	536
266040	266569	537
266570	267099	538
267100	267630	539
267631	268160	540
268161	268691	541
268692	269221	542
269222	269752	543
269753	270282	544
270283	270813	545
270814	271343	546
271344	271874	547
271875	272405	548
272406	272936	549
272937	273466	550
273467	273997	551
273998	274528	552
274529	275059	553
275060	275590	554
275591	276121	555
276122	276652	556
276653	277183	557
277184	277714	558
277715	278245	559
278246	278776	560
278777	279307	561
279308	279838	562
279839	280369	563
280370	280901	564
280902	281432	565
281433	281963	566
281964	282495	567
282496	283026	568
283027	283557	569
283558	284089	570
284090	284620	571
284621	285152	572
285153	285683	573

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
285684	286215	574
286216	286746	575
286747	287278	576
287279	287810	577
287811	288341	578
288342	288873	579
288874	289405	580
289406	289937	581
289938	290468	582
290469	291000	583
291001	291532	584
291533	292064	585
292065	292596	586
292597	293128	587
293129	293660	588
293661	294192	589
294193	294724	590
294725	295256	591
295257	295788	592
295789	296320	593
296321	296853	594
296854	297385	595
297386	297917	596
297918	298449	597
298450	298982	598
298983	299514	599
299515	300046	600
300047	300579	601
300580	301111	602
301112	301644	603
301645	302176	604
302177	302708	605
302709	303241	606
303242	303774	607
303775	304306	608
304307	304839	609
304840	305371	610
305372	305904	611
305905	306437	612

# of donors at center		Max. # of pos. donors (Alert Level)
From	To	
306438	306970	613
306971	307502	614
307503	308035	615
308036	308568	616
308569	309101	617
309102	309634	618
309635	310000	619