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Guideline on epidemiological data on blood transmissible infections

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Comments should be provided using this template. The completed comments form should be sent to BWPSecretariat@ema.europa.eu

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Guideline on epidemiological data on blood transmissible infections

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Executive summary

This guideline (EMA/CHMP/BWP/548524/2008) outlines the scientific data requirements for epidemiological data on blood transmissible infections to be included in applications for Plasma Master File certification submitted to the EMA. It is a new revision of the CHMP/EMA Plasma Master File epidemiology guideline (EMEA/CPMP/BWP/125/04) which came into operation in July 2005.

1. Introduction (background)

Applicants for Plasma Master File (PMF) certification are required to include epidemiological data on the local viral epidemiology for each blood/plasma centre listed in the PMF application.

The revision of this guideline follows an earlier revision of this guideline which came into effect in 2011. It was recognised in the meantime that a further revision was needed based on the experience of data submission and evaluation.

The present document represents a revision of the “Guideline on epidemiological data on blood transmissible infections” which was undertaken by experts appointed by the CHMP/BWP who took into account both the results of a public consultation and additional experience acquired from the evaluations of the epidemiological data submitted by applicants for EMA PMF certification.

2. Scope

The guideline outlines the scientific data requirements for epidemiological data (including collection, collation, use for the calculation of epidemiological parameters such as incidence and prevalence rates, and interpretation) for applications to the EMA for PMF certification, re-certification and variation, as appropriate.

The scope of the revision is to provide additional guidance to PMF holders on:

- Residual risk calculation - HBV adjustment factor, first time tested donor adjustment factor, and window periods used in calculations.

- Extension of the trend analysis period to more than 3 years now that data is available over longer periods in the format required by the guideline.

- The usefulness of graphical representations of trends and control charts for the presence of trends for organisations/countries

- Approaches to identify trends on a centre basis

- “Epidemiological data requirements for approval of blood establishments”, which will facilitate the evaluation of epidemiological data of new PMF Blood establishments and adequate selection of the appropriate donor population and blood supply.

3. Legal basis

Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use introduces the concept of the PMF. Part III, section 1.1 of Annex I lays down specific requirements related to the PMF and states that “For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3, the dossier requirements mentioned in "Information

related to the starting and raw materials", for starting materials made of human blood/plasma may be replaced by a PMF certified in accordance with this Part". It also states that "In accordance with the provisions of Article 109, as amended by Directive 2002/98/EC, which refers to the requirements for donors and the testing of donations, the Plasma Master File shall include information on the plasma used as starting/raw material". Epidemiological data on blood transmissible infections are part of the information required.

Data on incidence and prevalence of transfusion transmissible infectious markers in donors of blood and blood components are also required as part of the annual reports of blood establishments (Annex II of Directive 2002/98/EC[1]).

4. Purpose

The requirement to collect epidemiological data on blood transmissible infections is intended to obtain information on the infection risk in a specific donor population and is thus an essential part of the measures taken to ensure an adequate selection of donors of blood and plasma. Adequate selection of donors is one of the important measures for the safety of plasma derivatives together with the virus testing of donations and pools, and the virus inactivation capacities of manufacturing steps. The purpose of collecting epidemiological data is to characterise the donor population with respect to infection risk, to allow detecting changes over time, and to allow comparison of risks between donor populations.

This is one of the measures to ensure that donations do not come from donors with a high probability of being infected with blood transmissible agents. Data on prevalence and incidence of blood transmissible infectious agents in donors and the estimated risk of infectious donations entering the plasma supply should be presented and discussed according to the present guidance.

The PMF is a document which is annually updated and which is subject to variations e.g. concerning the approval of blood establishments for inclusion into a PMF. Continuous epidemiological evaluation at individual blood/plasma collection centres together with an annual update is therefore required.

5. Infectious disease markers

Epidemiological data should be collected on those blood-borne infectious agents for which a potential transmission by blood products is well recognised and routine testing of blood and plasma donations is mandatory. These infectious agents currently include human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). The principles which underlie the testing for the markers for these viruses also apply to the collection of epidemiological data. Currently the minimum data collected cover anti-HIV 1+2, anti-HCV and hepatitis B surface antigen (HBsAg) test results, while the PMF holder should also report separately the results of additional screening tests[a] (e.g. NAT assays). Clearly, a donor tested positive for a specific virus by both serological and NAT tests should be reported as a single case according to the relevant definition below.

[a] Data on anti-HBc are not specifically required

Only confirmed infections should be reported using the following definition[2]:

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 second NAT test or later serology.

"NAT only positives" are in most cases indicative of recent infection and should, therefore, be reported separately from "Confirmed seropositives". Donations that are reactive in the initial screening tests but negative or indeterminate in confirmatory tests, should not be included as positives.

Reporting of confirmed cases will reflect truly positive donors/donations rather than limitations in the specificity of the testing system. If donors are excluded from the donor population on the basis of a positive NAT test without a confirmatory test being performed, these data should also be reported, but separately from the data on confirmed positives. In all cases the companies should clearly explain their approach and criteria for excluding donors.

Further practical details for reporting data are set out in Section 8.

6. Donor classifications

The Council Recommendation on the suitability of blood and plasma donors and the screening of donated blood in the European Community (98/463/EC)[3] provides the following definitions of types of donors:

Prospective donor	Someone who presents himself/herself at a blood or plasma collection establishment[b] and states his/her wish to give blood or plasma.
First time donor	Someone who has never donated either blood or plasma.
Repeat donor	Someone who has donated before but not within the last two years in the same donation centre.
Regular donor	Someone who routinely donates their blood or plasma (i.e. within the last two years), in accordance with minimum time intervals, in the same donation centre.

It is not the aim of the exercise to acquire information on individuals who express an intention to donate, or individuals present in a collection centre without being tested. In order to get information on the prevalence and incidence of viral infections in the donor populations of individual collection centres, a test result for the viruses of interest needs to be available. **Therefore, for the purpose of the assessment of epidemiological data of donor populations, the following definitions are used in this document[c]:**

[b] Blood establishments are defined in Directive 2002/98/EC[1] as "any structure or body that is responsible for any aspect of the collection and testing of human blood or blood components, whatever their intended purpose, and their processing, storage and distribution when intended for transfusion. This does not include hospital blood banks." The use of the term "collection centre" in this guideline means a specific site where blood/plasma is collected, including any associated mobile sites.

[c] Similar definitions are used in the Council of Europe Questionnaire on the collection, testing and use of blood and blood products in Europe.

First time tested donor	Person 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	Person whose blood/plasma has been tested previously for infectious disease markers in a given blood system.

A given blood system means a system that has records of whether a donor has donated before and the results of previous testing.

7. Prevalence and incidence

This section first describes the general concepts of incidence and prevalence for infectious diseases and then the application of these concepts in the study of blood/plasma donor population.

Prevalence and incidence can be defined as follows:

Prevalence	Frequency of infection identified (including both past and recent infections) at a specified point in time or over a specified time period in a defined population.
Incidence	Rate of newly acquired infection identified over a specified time period in a defined population.

Incidence is the measure of new infections and prevalence is a measure of the extent of infection in a population.

Prevalence and incidence are complementary in that they provide information on past and current risk of infection in the population.

-High prevalence and incidence is indicative of established infection with continuing transmission.

-High prevalence and low incidence is indicative of established infection but with intervention measures (e.g. education on risk of infection, effective therapy) having been introduced.

-Low prevalence and high incidence indicates infection which is probably recently introduced into the population.

-Low prevalence and incidence would indicate that there is little or no evidence of past or current infection.

Clearly while the first and third scenarios could be considered to be a high risk population, and the 4th scenario would indicate a low risk population, high prevalence and low incidence may be medium risk since established infection may create a reservoir from which future new infections (incidence) may arise.

There are certain characteristics of the blood/plasma collection system that need to be taken into account when parameters are defined for the collection of epidemiological data[4, 5, 6, 7, 8, 9]:

-Prevalence data in donors tested for the first time provide information on the population presenting to become blood/plasma donors and who have not deferred themselves through the donor questionnaire.

Determination of incidence is important because newly infected donors who are in the “window period” (i.e. donors whose recent infection is not recognised by the applied tests) may donate infectious blood or plasma.

In the context of the study of a donor population;

1. Prevalence can be defined as **(formula 1)**:

$$\frac{\text{No. of positive donors in a specified period}}{\text{Total No. donors in the same specified period}} \times 100{,}000^{d}$$

Since prevalence in "first time tested donors" is known to be different to prevalence in "repeat tested donors", it is recommended that these are reported separately (see Section 8).

2. Incidence can be measured in "repeat tested donors" as **(formula 2)**:

$$\frac{\text{No. of positive repeat tested donors with a previous negative donation in the study period}}{\text{The sum of the time between the first and the last test result of every donor during the study period}^{f} \text{ (= person-years at risk)}} \times 100{,}000^{e}$$

In the case of HBsAg, an adjustment is needed to get an estimation of true incidence (see also 10).

In practice, the data required to determine incidence according to the above definition are difficult to obtain because the intervals between the first and last donation/test sample of every individual donor during the study period have to be known for a large numbers of donors.

According to literature[10] an alternative approach to **estimate** incidence is as **(formula 3)**:

$$\frac{\text{No. of positive repeat tested donors in the study period with a previous negative donation}}{\text{The total No. of donations from repeat donors in the study period x mean interdonation interval (expressed in years) (= person-years at risk)} \ ^{(*)}} \times 100{,}000$$

(*) The number of person years can be estimated by dividing the number of donations from repeat donors by the average annual number of donations per repeat donor, i.e. the denominator can be expressed as:

$$\frac{\text{Total No of donations from repeat donors in the study period}}{\text{No of donations / (No of repeat donors x time period (years))}}$$

If the calculation was to be made over one calendar year, the denominator of formula 3 would then equal the number of repeat donors in a calendar year (expressed as person-years). In practice, the calculation would equal the rate of positive "repeat tested donors" in a calendar year (see Section 8.2 below).

Important note: *In the calculation of "positive repeat tested donors in the study period with a previous negative donation", the previous negative test result does not have to be in the same study period (e.g. a donor that only donates once during the study period would be included provided that the donor's blood/plasma has been tested at some time in the past in the given blood system).*

If formula 2 or 3 are not used, the alternative algorithm should be clearly defined and justified and a literature reference should be given by the PMF Holder.

3. Incidence in "first-time tested donors"

[d] Prevalence is often expressed per 100,000 donors.
[e] Incidence is often expressed per 100,000 person-years at risk.
[f] Expressed in years (or fraction of a year).

Incidence in "first-time tested donors" for HIV can be estimated using a sensitive/less-sensitive-test approach[6], where newly acquired infections are identified on the basis of a positive result with a sensitive test and a negative result with a less sensitive serological test. A modification of this approach uses NAT as the sensitive test, both for HIV and HCV[9]. (See also section 10.)

8. Reporting of overall epidemiology data on infectious disease markers in donor population

In reporting epidemiological data it is important to clearly describe the testing result definition and the classification of the donor as this will affect the results obtained and the comparability of data.

For each organisation responsible for collecting blood or plasma, the donor population which actually donates into the plasma pool should be described including information on how many donations are collected on average from one donor per year (frequency of donations), and on whether donations from first time tested donors are used in plasma pools.

As a result of the screening programme, a donor might be defined as "positive" for a certain virus based on different approaches (e.g. repeatedly reactive (= 2 times reactive) in a screening test, confirmed seropositive, NAT only positive, or NAT positive but not confirmed by follow-up investigations). Only "confirmed seropositives" and "NAT only positives" should be reported; the PMF Holder should provide a statement on the confirmation strategy for reactive test results obtained in the serological tests. NAT only positives should be reported separately from serological testing results, as outlined in Tables 1 and 2 in the Appendix. If confirmatory testing has not been done following NAT reactive results these data should be reported separately (See also Section 5 of this guideline.)

The potential risk for plasma-derived products arises from undetected infectious donations entering the plasma pool. A viraemic donor may donate once or several times during the "window period", i.e. the period of infection when the infected (and viraemic) donor is tested negative by screening tests. Therefore, in order to facilitate the risk assessment the number of donations collected should also be reported (see section 10 below).

Data should be reported per country, per organisation and per individual collection centre, and per calendar year (January-December) using the tabular formats given in Tables 1 and 2 in the Appendix of this guideline (Ref. EMA/219007/2015). The data should be reported for the current year and the three previous years. If a country is collecting both whole blood recovered plasma and plasmapheresis plasma data should also be summarised separately for each of these two categories. In order to facilitate a relative assessment of these data, the data should be presented in absolute numbers and calculated per 100,000 donors.

8.1. "First time tested donor" population

According to the definition in Section 6, "first time tested donors" are persons who are tested for the first time (with or without donation) and without evidence of prior testing in a given blood system. For companies using the applicant/qualified donor system[g], the "first time tested donor population" represents a sub-set of "applicant donors" (i.e. "applicant donors" that are tested for the first time in a given system).

[g] **Qualified donor**: Individuals who have been qualified for continued donations by passing two donor screenings and two sets of serological viral testing for HIV, HBV and HCV within six months, with a minimum interval between the screenings according to national recommendations or requirements. **Applicant donor:** A donor going through the testing to become a qualified donor. Donations from an applicant donor are held in quarantine until cleared by an acceptable qualifying donation.

Prevalence in "first time tested donors" in a given period (formula 4):

$$\frac{\text{No. of positive "first time tested donors" in a calendar year}}{\text{Total No. of "first time tested donors" in the same calendar year}}$$

8.2. "Repeat tested donor" population

As described in Section 6, a "repeat tested donor" is a person whose blood/plasma has been tested previously for infectious disease markers in a given blood system. This includes "regular donors" and "repeat donors". For companies using the applicant/qualified donor system, this includes "applicant donors" tested for a second time, "applicant donors" requalifying after an interval of 6 months or more, and "qualified donors".

Rate of positive "repeat tested donors" in a given period[h] (formula 5)

$$\frac{\text{No. of positive "repeat tested donors" in a calendar year}}{\text{Total No. of "repeat tested donors" in the same calendar year}}$$

Important note: *the previous negative test result does not have to be in the same calendar year (e.g. a donor that only donates once during the calendar year would be included provided that the donor's blood/plasma has been tested at some time in the past in the given blood system).*

9. PMF Holder`s assessment of epidemiological data: monitoring change and alert limits

The PMF Holder should assess the epidemiological data and the changes over time. The purpose is to identify collection centres with rates of infectious markers outside the normal range for the given donor population in the PMF and discuss any overall changes in the rates in (parts of) the donor population. The PMF Holder may assess changes over time and compare infections in the donor population with the use of control charts.

Any trend observed in the results introduced by new or additional screening tests (e.g. NAT assays) should be included in the assessment and discussed.

An example of a test to detect trends and a test for comparison of centres has been published[8].

Furthermore, alert limits should be defined to allow identification of outlier centres characterized by viral marker rates clearly outside the normal range of the given donor population(s) in the PMF.

In addition, also the effectiveness of remedial corrective actions for blood/plasma collection centres, which have been previously identified above the alert limits, should be discussed and assessed.

For a particular organisation/country demonstrating a significant higher prevalence/incidence than other organisations/countries in the PMF, a comparison with the general population might be valuable for the evaluation of the data.

[h] This is not strictly prevalence of infection in the population because as soon as an infection is detected, the donor is excluded from the population

Monitoring change

A comparison of the epidemiological data for the year under reporting with epidemiological data from previous years should be made for the individual collection centres, organisations and countries. Control charts may be used for analysis of kinetics of infection rates over the period of several years.

Organisations and countries

Control charts or other graphical tools should be submitted for each country and organisation included in the PMF, to facilitate the assessment and comparison of the kinetics of infection rates in the donor populations. Control charts should be provided for repeat tested donors (RT donors) and first time tested donors (FTT donors) separately over a period of several years (> 5 years) as far as these data are available. If a country is collecting both whole blood recovered plasma and plasmapheresis plasma it is strongly recommended to monitor changes separately, unless otherwise justified.

In the case of obvious upward trends over time for the country or organisation level, an analysis of potential reasons and respective interpretation of the data is expected.

Individual collection centres

Obvious upward trends in individual collection centres should be discussed as well.

Control charts can be useful tools as part of the quality management system. The control charts of individual collection centres represent the annual infection rates and also provide an upper limit calculated on all donations of the respective region collected over several years (e.g. 3x SD). Centres exceeding this upper limit are identified by the PMF holder and monitored. Separate upper limits are set for FTT donors and RT donors.

Note: The upper limit for individual collection centres, discussed in this section, is different to the alert limit discussed in the next section, and intended to identify centres showing an upward trend.

Alert limits

The criteria in place used by the PMF Holder to establish alert limits for epidemiological data, and the system to identify individual blood/plasma collection centres reporting data above the alert limits, should be described. The exceeding of alert limits should trigger corrective actions. The alert limits should be set to allow identification of outliers i.e. centres with viral marker rates clearly outside the normal range for the respective donor population in the PMF. Separate alert limits should be set for FTT donors and RT donors. Whereas alert limits for FTT donors have a function of setting criteria for anomalies with regards to prevalence, alert limits for RT donors serve the primary purpose of identifying outliers of incidence. In order to establish limits that are sufficiently discriminating for incidence, the basis for calculation should be kept separate from FTT data.

All centres exceeding the alert limit should be included in a respective overview. Potential reasons for the epidemiological situation in these centres should be discussed, also taking into account previous years of reporting. Corrective actions taken should be described, and the outcome of corrective actions should be described and discussed as far as respective data are available. This may also include more recent follow-up data to the annual update under assessment.

In the case that an individual collection centre has exceeded the established alert limits for the donor population in the PMF, it would be useful to include the individual centre control chart as part of the discussion.

10. Risk estimation of undetected infectious donations in routine testing

Introduction

A generic approach to present and perform calculations necessary to estimate the risk of undetected infectious donations is provided in this section. The proposed calculation is a simplified worst-case approach. However, PMF holders are encouraged to use the method described to facilitate assessment of the results. Any alternative method used needs to be fully described and appropriately justified. Sufficient detail should be provided to enable the calculations to be reproduced by a reader of the PMF. Guidance on reporting the results of the risk estimate is provided in section 11.

10.1. Window period risk model

As a standard risk estimate method, PMF holders are advised to use the basic "incidence" method[4, 10]. This method can be used to estimate the probability that an infected donor gave a donation with a negative result for the test in use, because of the recency of infection. This is referred to throughout this document as the "window period risk", and can be calculated according to (**formula 6**):

Window period risk for infection Y	=	Incidence in "repeat tested donors" of infection Y	x	viraemic window period of routine tests for Y (expressed in years)

The risk is estimated as the product of the incidence (expressed according to formulas 2 or 3) and the time interval in which a new infection would pass undetected (expressed in years). The result should be multiplied by 10, as it is common and advisable to report the risk per million donations, as specified in Table 4.

Incidence

Incidence in "repeat tested donors" in the year under review is calculated using formula 2, as in Schreiber *et al*[4,7], or alternatively is estimated using formula 3. In case no infections in "repeat tested donors" were detected in this year, the time period should be extended to previous years up to and including the last year in which an infection was reported. Incidence in "first time tested donors" can be deduced from the incidence in "repeat tested donors", see section 10.2.

Window period

The window period is a justified estimate of the time period in which a test method is unable to detect an infection in a donation because the viral load is below the methods' limit of detection. If more than one test is routinely applied to all donations, e.g. anti-HCV and HCV NAT, the shorter window period can be used.

Typically, the length of the window period for NAT is shorter than for serological testing: hence a larger reduction in risk is generally expected and achieved by NAT. As a worst case scenario, the viraemic portion of the window period with virus concentration below the sensitivity level of screening assays can be estimated by using viral replication kinetics and less sensitive testing scenarios, as provided in plasma master files for some organisations in the past. This scenario implies for HIV and HBV less sensitive minipool NATs with only marginal additional benefit when compared to CE-marked antibody (HIV) or HBsAg (HBV) tests. For HCV, minipool NAT has more relative benefit because of the anti-HCV non-reactive plateau phase with high HCV concentration during early infection phase.

For worst case residual risk calculations the following viraemic portions of window phases may be taken:

HCV: 8 days

HIV: 15 days

HBV: 35 days

The basic “incidence” method described in this section can (overestimate or underestimate) the “window period risk” if the interdonation interval of donors who acquire new infections is significantly different (longer or shorter) than the interdonation interval for all other donors. More specifically, the risk may be overestimated when the interdonation interval of donors who acquire new infections is significantly longer than the interdonation interval of non-seroconverting donors. In this case, it is desirable that PMF holders report a) the median interdonation intervals for their “repeat tested donors” who acquire a new infection, and b) the mean interdonation intervals for all “repeat tested donors”, and to comment on the likely over-estimation of risk if these intervals differ markedly (i.e. by ~20% or more). Otherwise, the overestimate may be considered as a worst-case.

10.2. The “new donor incidence adjustment factor” model

To estimate the risk of undetected infectious donations in “first time tested donors” according to the formula in 10.1, an estimate of the incidence in “first time tested donors” is required. This estimate can be obtained from the incidence in “repeat tested donors” multiplied by a factor that represents the relative risk of new infections amongst “first time tested donors” compared to “repeat tested donors”.

In scientific literature there are different approaches for determining incidence of infections in “first time tested donors”, mainly for HIV and HCV. However, HBV has similar transmission routes as HIV and HBV. Based on scientific publications on incidence in donor populations, PMF holders may use for the residual risk calculations an assumed threefold higher incidence for each of the virus infections in “first time tested donors” compared to “repeat tested donors”.

FTT donor incidence adjustment factor: 3

Any alternative “new donor incidence adjustment factor” chosen by a PMF holder should be based on a justified, local measure of the risk of new infection in “first time tested donors” [9, 11, 12, 13, 14, 15, 16, 17].

10.3. The HBV incidence adjustment factor model

The HBV incidence calculations should be adjusted for the transient nature of HBV infection, i.e. for the probability that a new HBV infection in a “repeat tested donor” has become undetectable by the time of his or hers first donation after acquiring HBV infection. As the presence of detectable amounts of HBsAg and HBV DNA in donations of HBV infected donors can both be transient, PMF holders are expected to use an HBV incidence adjustment factor for incidence estimates based on serology or NAT testing.

The value of this adjustment factor depends on:

a) the time period during which markers for HBV infection can be detected in plasma from HBV infected adults and

b) the interdonation interval (IDI) [18, 19, 20, 21, 22] For the calculation of the “window period risk”, it is advised to use a worst-case estimate of the adjustment factor for HBV incidence based on the assumptions used by Korelitz *et al*[18].

Korelitz *et al* assumed that:

- 70% of infected donors would have transient antigenaemia (lasting an average of 77 days - Seed *et al*[22]) , that

- 25% of infected donors would have no antigenaemia and that

- 5% would have persistent antigenaemia.

The probability of detection of HBV infection by HBsAg testing in these different groups is 77/IDI (transient antigenaemia), 1 (persistent antigenaemia), and 0 (no antigenaemia). The overall probability of detection can be calculated using **formula 7**, which takes into account the probability of detection and the relative contribution for the different groups.

formula 7: Probability of detection by HBsAg testing = (5%x1) + (70%x (77/IDI)) + (25%x0)

The HBV incidence adjustment factor can be calculated as 1/ Probability of detection by HBsAg testing.

As a worst case estimate, it is assumed that a donor donates once every six months, resulting in an HBV incidence adjustment factor of 2.9 to be used in the calculation of the risk estimate(s). For donor populations with an IDI ≤ 77 days the transient nature of HBV infection is not relevant. In this case an HBV incidence adjustment factor of 1.3 can be used, only taken into account the absence of antigenaemia in 25% of the population (see formula 7).

10.4. Method to calculate the risk due to inabilities or failures of testing systems to detect established infections

There is a risk of infectious donations passing undetected through routine testing due to inabilities or failures of the testing systems to detect established (prevalent) infections. For each individual virus and test system reported the risk of releasing a truly positive donation is a function of the *sensitivity* of the tests, the *risk of errors* in the testing system, and the prevalence of the infection amongst donors.

The risk of releasing a truly positive donation can be estimated for any given test system as (**formula 8)**[23]**:**

$$\text{Risk} = \left[\frac{\text{1-sensitivity}}{\text{sensitivity}} + \left(1 - \frac{\text{1-sensitivity}}{\text{sensitivity}}\right) \times \text{error rate} \right] \times \text{Prevalence}$$

Generally with state of the art methods, this risk is a direct function of the prevalence of infections amongst tested donors and is small compared to the risk of passing of 'window period' donations. Therefore, PMF holders are not required to provide quantitative estimates of the risk due to prevalent infections. However, if PMF holders are using donations with a relatively high prevalence (e.g. for new donors, tabulated in Tables 1 and 2 of the Appendix) this risk should not be neglected and should be addressed in the Overall Safety Strategy.

11. Reporting and interpretation of "worst case" risk estimates

When using the method recommended in section 10 of this guideline, the reporting details in Table 3 in the Appendix should suffice to describe the PMF holder's calculations performed to estimate the risk of undetected infectious donations. If an alternative method is used, sufficient detail should be provided to enable the calculations to be reproduced by a reader of the PMF.

The calculation performed for the risk estimate should represent a reasonable "worst case" situation. In applications covering very diverging plasma sources and/or testing strategies it might be appropriate to perform and present different potential worst case calculations, for example a "worst case" risk estimate for plasmapheresis donors from one collection organisation picked based on relatively high incidence in repeat tested donors and a "worst case" risk estimate for whole blood donors from one collection organisation picked based on relatively high incidence and/or the use of first time tested donors with relatively high prevalence.

The criteria used for the definition of the "worst case(s)" should be described and justified by the applicant. Criteria to be taken into account when performing this exercise include for example the epidemiological situation (prevalence and incidence), the use of plasma from first time tested donors, the presence/absence of additional voluntary tests, significant differences in test sensitivities or pool sizes. If deemed necessary additional scenarios and their respective estimates will be requested from the applicants during the evaluation period.

The results of the calculations should be reported using the tabular format in Table 4 in the Appendix. The risk estimates should be reported separately for HBV, HCV, and HIV by calendar year, per million donations. If donations from first time tested donors are used this should be included in the overall estimation of the risk, as well as being presented separately.

Interpretation of the risk estimates requires understanding of the range of uncertainty around the point estimate and this should be discussed in the dossier.

The additional application of risk-reduction measures to the plasma supply post donation screening (e.g. inventory hold, look-backs, or further NAT testing of manufacturing plasma pools) is not to be included in the risk estimate. These additional measures and their impact on the reduction of risk of plasma supply should be presented in the overall safety strategy described in section 1.2 of the Guideline on the scientific data requirements for a Plasma master File (PMF) Revision 1 EMEA/CHMP/BWP/3794/03.

The potential viral load in representative manufacturing pool(s) should be calculated based on the results of the risk estimate(s).

12. Epidemiological data requirement for approval of blood establishments

The PMF is a document which is annually updated and which is subject to approval of blood establishments (BE I, BE II, BE III) for inclusion into a PMF. To avoid procedural obstacles and to facilitate the approval of blood establishments PMF holders should provide appropriate epidemiological data with their applications.

The acceptance of blood establishments is based on epidemiological data already available in a PMF and the function and responsibility of the blood establishment concerned.

The blood establishments (BE) have been categorised according to their function and responsibility as follows:

BE-I: Responsibility for all aspects of collection and testing of blood components for all purposes including transfusion. Does not cover hospital blood banks.

BE-II: Actual collecting site + storage, separation and freezing only. No testing.

BE-III: Collection only

The following requirements have been considered the minimum which should be available at the time of filing for approval of new blood establishments.

For a new BE in a country which is new for a particular PMF at least 6 months epidemiological data from a significant number of donors should be provided. The epidemiological data obtained should be compared to infection rates in the new country and to infection rates in other BEs already approved in the concerned PMF. For a new BE-I in a country already included in the concerned PMF, epidemiological data for at least 6 months should be provided at the time of application. The epidemiological data obtained should be compared to infections in other BEs already approved in the concerned PMF.

A new BE-II or BE-III in a country already included in the concerned PMF could be accepted without submission of epidemiological data, depending on the justification of the PMF holder. However, based on the geographical situation and/or the epidemiological situation of the area where the new BE-II and/or BE-III are located, 6 months epidemiological data may be required. This may be relevant for large countries such as the USA.

If a BE-I, BE-II or BE-III has already operated for some time, all available data for up to 4 years including a trend analysis should be submitted.

If the viral marker rates for the BEs applied for are out of the range compared to the other BEs already approved in the concerned PMF (e.g. higher rates FTT donors, higher rate NAT only positives), a risk assessment should be provided together with a justification of acceptance of the new BE(s).

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