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Guideline on epidemiological data on blood transmissible infections

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Note:

1. This Guideline should be read together with the appendices published in this link: EMA/735037/2015 Rev.1

2. This revised guideline uses the terms Blood establishment and centres, i.e. the term "organisation" has been replaced with "blood establishments" to be consistent with the "*Guideline on the scientific data requirements for a Plasma master File (PMF) Revision 1 EMEA/CHMP/BWP/3794/03*".

Keywords	**PMF, epidemiology, first time tested donors, repeat tested donors, prevalence, incidence, residual risk, risk estimate, control charts, trends.**

Guideline on epidemiological data on blood transmissible infections

Table of contents

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. The revision of this guideline follows an earlier revision of this guideline (EMA/CHMP/BWP/548524/2008) which came into effect in 2011 and superseded the guideline, which came into operation in July 2005 (Ref. EMEA/CPMP/BWP/125/04).

1. Introduction (background)

Applicants for Plasma Master File (PMF) certification are required to include the donor population epidemiological data on blood transmissible infections for each individual blood/plasma collection centre[a] and blood establishment[b] listed in the PMF application.

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 of data 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 objective of the revision is to provide additional guidance to PMF holders on:

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

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

- The usefulness of control charts (or other graphical tools) to identify the presence of trends in viral marker rates for blood establishments[b]/countries.

- Approaches to identify trends in viral marker rates on an individual collection centre basis.

- Epidemiological data requirements for approval of blood/plasma collection centres and blood establishments, which will facilitate the evaluation of epidemiological data of new PMF Blood establishments and adequate selection of the appropriate donor population.

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[a] Centre is defined as "*collection site or premise where blood or plasma is collected (and may also be processed and stored)*" in the Guideline on the scientific data requirements for a plasma master file (Doc. Ref. EMEA/CHMP/BWP/3794/03 Rev.1). *The use of the term "collection centre" in this guideline means a specific site where blood/plasma is collected, including any associated mobile sites.*

[b] "Organisations" replaced with the term "blood establishments" as defined in Directive 2002/98/EC "*any structure or body that is responsible for any aspect of the collection and / or 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.*"

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 blood and plasma donors. 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 reduction capacities of manufacturing steps. The purpose of collecting epidemiological data is to characterise the donor population with respect to infection risk, to allow detecting epidemiological 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. Continuous epidemiological evaluation at individual blood/plasma collection centres together with an annual update of the PMF documentation is therefore required. 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 also subject to variations e.g. concerning the approval of new blood/plasma centres and blood establishments for inclusion into the PMF and epidemiology information in that specific donor population should be submitted (see section 12).

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.

While currently, the minimum data collected cover anti-HIV 1+2, anti-HCV and hepatitis B surface antigen (HBsAg) test results, the PMF holder should also report separately the results of additional screening tests[c] (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.

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, or on the basis of non-confirmed reactive serological test results, these data should also be reported, but separately from the data on confirmed positives. In all cases the PMF holders 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 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 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

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[c] Data on anti-HBc are not specifically required.

assessment of epidemiological data of donor populations, the following definitions are used in this document[d]:

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.

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

2. 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.

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

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

Clearly while the 1st and 3rd scenarios could be considered to be indicative of a high risk population, the 2nd scenario may imply medium risk since established infections may create a reservoir from which future new infections may arise, and the 4th scenario would indicate a low risk population.

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]:

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

-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. <u>Prevalence</u> can be defined as:

(formula 1):
$$\frac{\text{No. of positive donors in a specified period}}{\text{Total No. donors in the same specified period}} \times 100,000^{e}$$

2. <u>Incidence</u> in "repeat tested donors" can be measured as:

(formula 2):
$$\frac{\text{No. of positive "repeat tested donors" with a previous negative donation in the study period}}{\text{The sum of the time between the first and the last test result of every donor during the study period}^{g} \text{ (= person-years at risk)}} \times 100,000^{f}$$

If HBsAg and/or HBV DNA are used as marker(s) for HBV infections, an adjustment factor may be needed to obtain an estimation of true incidence, as the presence of detectable amounts of these markers in donations of HBV infected donors can be transient (see also Section 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 number of donors.

According to published literature[10], an alternative approach to estimate incidence "in repeat tested donors" is as:

(formula 3):
$$\frac{\text{No. of positive "repeat tested donors" in the study period with a previous negative donation}}{\text{Total No. of donations from "repeat tested donors" in the study period x mean interdonation interval (IDI) (expressed in years)}} \times 100,000$$
$$(= \text{person-years at risk)}^{(*)}$$

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

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

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

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

the "incidence" calculation would equal the rate of positive "repeat tested donors" in a calendar year (see formula 5 Section 8.2).

Important note: *In the calculation of No. 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 point 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. <u>Incidence</u> in "first time tested donors"

In "first time tested donors" incidence may be estimated by differential serological testing, e.g. using a combination of sensitive and less-sensitive antibody tests for HIV[6]. Newly acquired (incident) infections are identified on the basis of a positive result with a more sensitive test combined with a negative result with a less sensitive serological test. Another approach uses NAT positive test results combined with a negative result in a serological screening test[9]. This approach is straightforward for HIV and HCV, while for HBV further differentiation between an incident and a so-called occult infection course is needed. Different investigations of blood donor populations suggest for worst case estimation of "first time tested donors" incidence the respective "repeat tested donors" incidence multiplied with an adjustment factor. (See also section 10.)

8. Reporting of epidemiology data on viral markers in donor population

In reporting epidemiological data, it is important to clearly describe the testing result definitions (see Section 5) and the donor classifications (see Section 6) as this will affect the results obtained and the comparability of data.

For each blood establishment, the donor population which actually donates into the plasma pool should be described. This should include information on how many donations are collected on average from one donor per year (frequency of donations), and information 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. The PMF Holder should provide a statement on the confirmation strategy for reactive test results (See also Section 5 of this guideline). If confirmatory testing has not been done these data should be reported separately. Only "confirmed seropositives" and "NAT only positives" should be reported. "NAT only positives" should be reported separately from serological testing results, as outlined in Tables 1 and 2 in the Appendix.

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

Data should be reported per country, per blood establishment 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/651459/2015). The data should be reported for the referenced year under reporting and the four previous years. In order to facilitate a relative assessment of these data, the data should be presented in absolute numbers and calculated per 100,000 donors. If both

whole blood recovered plasma and plasmapheresis plasma are collected, data should also be summarised separately for each of these two categories.

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 for infectious disease markers (with or without donation) and without evidence of prior testing in a given blood system"*.

For PMF holders using the applicant/qualified donor system[h], 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*).

Prevalence in "first time tested donors" in a specified period:

(formula 4):

$$\frac{\text{No. of positive "first time tested" donors in a calendar year}}{\text{Total No. of "first time tested donors" in the same calendar year}} \times 100,000^{[i]}$$

For the purpose of the PMF data submission, the calculation is presented over 1 calendar year (see Table 1, in appendix).

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 PMF holders using the applicant/qualified donor system, "repeat tested donors" includes "applicant donors" tested for a second time, "applicant donors" requalifying after an interval of 6 months or more, and "qualified donors".

As explained in section 5, if the calculation of "incidence" in "repeat tested donors" is made over 1 calendar year, the calculation would equal the rate of positive "repeat tested donors" in a calendar year:

Rate of positive "repeat tested donors" in a given period

(formula 5):

$$\frac{\text{No. of positive "repeat tested donors" in a calendar year}}{\text{Total No. of "repeat tested donors" in the same calendar year}} \times 100,000^{[i]}$$

For the purpose of the PMF data submission, the calculation is presented over 1 calendar year (see Table 2 in appendix).

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 point in the past in the given blood system).*

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[h] **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.
[i] This is often expressed per 100,000 donors.

9. PMF Holder`s assessment of donor population epidemiological data: monitoring change over time 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 viral markers outside the normal range for the given donor population in the PMF and to discuss any overall changes in the rates in (parts of) the donor population. The PMF Holder may assess changes over time and compare viral marker rates 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 also be included in the assessment and discussed.

Furthermore, alert limits should be defined with the purpose to allow identification of outlier of individual collection centres characterised by rates of viral markers outside the normal range of the given donor population(s) in the PMF.

In addition, for individual collection centres, which have been identified above the alert limits, the remedial corrective actions taken should be described, and their effectiveness, discussed and assessed.

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

Monitoring change

A comparison of the epidemiological data for the referenced year under reporting, with data from all previous years as far as data are available, should be submitted for the individual collection centres, blood establishments and countries. Control charts (or other graphical tools) may be used to monitor changes overtime.

- Blood establishments and countries
Control charts (or other graphical tools) should be submitted for each country and blood establishment included in the PMF, to facilitate the assessment and comparison of the changes over time of viral markers rates in the donor population. Data should be included for the referenced year under reporting and all previous years, as far as these data are available.

Control charts (or other graphical tools) should be provided for "repeat tested donors" and "first time tested donors" separately. If in a blood establishment and/or country both whole blood recovered plasma and plasmapheresis plasma is collected, it is strongly recommended to monitor changes separately, unless otherwise justified.

In case obvious upward trends are observed over time for a country or blood establishment, an analysis of the potential reasons and respective interpretation of the data should be provided.

-Individual collection centres
Any obvious upward changes shown over time, for one or more viral markers' rates in individual collection centres, should be discussed.

Control charts (or other graphical tools) to represent the annual viral markers' rates of individual collection centres can be useful tools as part of the quality management system. They may also be used to identify those centres that show obvious changes over time for one or more viral markers' rates.

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 rates of viral markers outside the normal range for the respective donor population in the PMF. Separate alert limits should be set for "first time tested donors" and "repeat tested donors". Whereas alert limits for "first time tested donors" have a function of setting criteria for anomalies with regards to prevalence (potentially associated with incidence), alert limits for "repeat tested 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 alert limits for "repeat tested donors" should be kept separate from "first time tested donors" data.

All centres exceeding the alert limit for one or more viral markers' rates should be discussed in an overview of the respective centres. In addition, the potential reasons for the epidemiological situation in these centres should be discussed, taking also into account all available data from previous reporting years. Corrective actions and their effectiveness should be described and discussed. This may also include more recent follow-up data during the procedure 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. Residual risk: Risk estimation of undetected viraemic donations in routine testing

Introduction

PMF holders are requested to provide estimates of the risk of viraemic donations passing undetected in routine testing, due to collection of donations with testing results that are truly negative to the tests in use (i.e. during the "window period" for the test in use, as further described below).

This section provides a generic approach to present and perform the necessary calculations to estimate the risk of undetected viraemic donations. The proposed calculation is a simplified worst-case approach and PMF holders should use the method described to facilitate assessment of the results. Any other approach needs to be fully described and appropriately justified and sufficient detail should be provided to enable the assessment of the calculations. Guidance on reporting the results of the risk estimate is provided in section 11.

10.1. Method to calculate "Window period risk"

As a standard approach, PMF holders are advised to use the basic "incidence" method [4, 10] to estimate the risk that an infected (potentially viraemic) donor would give a blood/plasma donation with a negative test result because of the recency of infection. This risk 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^j = Incidence[k] in "repeat tested donors" of infection Y x viraemic window period of routine tests for infection Y (expressed in years)

The risk is estimated as the product of the incidence 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 reporting is estimated using formula 5. 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.

For HBV, the use of the "HBV incidence adjustment factor" is recommended (see section 10.3.)

The estimation of the "window period risk" in "first time tested donors" can be deduced from the incidence in "repeat tested donors" with a "first time tested donor adjustment factor" as recommended in section 10.2.

- *Window period*

The window period is a justified estimate of the time period (length) in which a test method is unable to detect 1) a recent infection because there is not yet virus in blood (non-viraemic phase), or 2) the virus load is below the methods' limit of detection of NAT or antigen testing (viraemic phase), or, where 3) NAT or antigen testing is not performed, the antibodies are not yet detectable in the testing method applied. 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 phase 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. This scenario implies that for HIV and HBV less sensitive NATs (e.g. testing of larger minipools as practised by some blood establishments), has only marginal additional benefit when compared to CE-marked antibody (HIV) or HBsAg (HBV) tests. For HCV, the minipool NAT has more benefit with high HCV concentration during early infection phase compared to the anti-HCV non-reactive plateau phase.

For the purpose of this guideline, for the worst case residual risk calculations, the following estimates of viraemic window periods are recommended to be used:

HCV: 8 days

HIV: 15 days

HBV: 35 days

According to formula 6 the value should be expressed in years.

For reasons outlined above, these worst case viraemic window periods are considered appropriate in case of both serology and NAT testing.

The "basic incidence" method recommended in this section can misestimate (overestimate or underestimate) the "window period risk" if the IDI of donors who acquire new infections is significantly different (longer or shorter) to the IDI for all other donors. More specifically, the risk may be overestimated when the IDI of donors who acquire new infections is significantly longer than the IDI of

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[j] Risk estimates should be reported separately for HBV, HCV, and HIV.
[k] This is expressed per 100,000 donors.

donors who did not acquire infections. In this case, it is desirable that PMF holders report a) the median IDIs for their "repeat tested donors" who acquired a new infection, and b) the mean IDIs for all "repeat tested donors", and comment on the likely overestimation 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. "First time tested donor" incidence adjustment factor

To estimate the residual risk of undetected infectious donations in "first time tested donors" in the window period, according to the formula 6 in section 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" of the same donor population multiplied by a factor (i.e. "first time tested donor incidence adjustment factor") that represents the relative risk of new infections amongst "first time tested donors" compared to "repeat tested donors".

Based on scientific publications on incidence in donor populations, PMF holders may use, for the "first time tested donors" residual risk calculations, an assumed threefold higher incidence, for each of the virus infections, in "first time tested donors" compared to "repeat tested donors".

"First time tested donor incidence adjustment factor": 3

Any alternative "First time tested 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. HBV incidence adjustment factor

The HBV incidence calculations should be adjusted for the transient nature of markers for 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 the HBV incidence 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 IDI [18, 19, 20, 21, 22]

As information on the presence of detectable amounts of HBV DNA in HBV infected persons is limited, for the calculation of the "window period risk", it is advised to use a worst-case estimate of the HBV incidence adjustment factor based on the assumptions used by Korelitz et al.[18].

Korelitz et al. assumed that:

- 5% would have persistent antigenaemia,

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

- 25% of infected donors would have no antigenaemia

The probability of detection of HBV infection by HBsAg testing in these different groups is 1 (persistent antigenaemia), 77/IDI (transient 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 antigenaemia 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] x100.

As a worst case estimate, it is assumed that a donor donates once every six months (i.e. IDI 180 days), resulting in an HBV incidence adjustment factor of 2.9 to be used in the calculation of the risk estimate(s).

HBV incidence adjustment factor (IDI 180 days) = [1/ (5%x1) + (70%x (77/180)) + (25%x0)] x 100]=2.9

For donor populations with an IDI ≤ 77 days, the probability of detection of transient antigenaemia is 1. In this case, an HBV incidence adjustment factor of 1.3 can be used, only taking into account the absence of antigenaemia in 25% of the population.

HBV incidence adjustment factor (IDI ≤ 77 days) = [1/ (5%x1) + (70%x1) + (25%x0)] x 100]= 1.3

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]:**

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

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" estimates of the "window period risk"

The 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 as per the method recommended in section 10.

The calculation performed for the residual 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 blood establishment selected on the basis of relatively high viral markers' rates in "repeat tested donors",

-a "worst case" risk estimate for whole blood donors from one blood establishment selected on the basis of relatively high viral markers' rates in "repeat tested donors" and/or the use of "first time tested donors" with relatively high viral markers' rates in "first time tested donors".

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 (viral markers' rates), the use of plasma from "first time tested donors", the presence/absence of additional voluntary tests, and significant differences in test sensitivities or pool sizes (number of donations pooled for testing). 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 plasma from donations from "first time tested donors" is used, the residual risk in "first time tested donors" should be presented separately as well as included in the overall estimation of the risk.

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 worst-case virus load in representative manufacturing pool(s) should be calculated and discussed based on the results of the risk estimate(s).

12. Epidemiological data requirement for approval of blood/plasma collection centres and blood establishments for inclusion in the PMF

At the time of filing for approval of new blood/plasma collection centres and blood establishments the following epidemiological data is considered as minimum:

For a new blood/plasma collection centre and/or blood establishments at least 6 months epidemiological data from a significant number of donors should be submitted. The epidemiological data should be compared to the rates of viral markers in the other collection centres already approved in the concerned PMF.

For a new blood/plasma collection centre and blood establishments in a country which is new for a particular PMF, the epidemiological data obtained should also be compared to the viral rates in the general population of the new country.

A new blood/plasma collection centre, within a blood establishments already included in the concerned PMF, could be accepted with less than 6 months submission of epidemiological data, provided satisfactory justification of the PMF holder is submitted. However, depending on the geographical

and/or the epidemiological situation of the area where the new blood/plasma collection centre is located, 6 months epidemiological data may still be required. This may be relevant for large countries.

If the blood/plasma collection centres and blood establishments applied for have already operated for some time, all available epidemiological data, including a trend analysis, should be submitted in accordance with the requirements of this guideline.

If the infection rates for the blood/plasma collection centres and blood establishments applied for are out of the range compared to the other collection centres and blood establishments already approved in the concerned PMF (e.g. higher rates "first time tested donors", higher rate NAT only positives), a risk assessment together with a justification for acceptance of the new blood/plasma collection centres/ blood establishments s should be provided.

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