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DRAFT

REVISION

GUIDELINE ON EPIDEMIOLOGICAL DATA ON BLOOD TRANSMISSIBLE INFECTIONS

(EMEA/CPMP/BWP/125/04. Rev 1)

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GUIDELINE ON EPIDEMIOLOGICAL DATA ON BLOOD TRANSMISSIBLE INFECTIONS (EMEA/CPMP/BWP/125/04. Rev 1)

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EXECUTIVE SUMMARY

In the light of experience gained with the application of the Guideline on Epidemiological data (published in Jan. 2005 http://www.emea.europa.eu/pdfs/human/bwp/012504en.pdf), a group of experts was assigned to critically look at the:

- 2006 epidemiological data submitted in the Plasma Master File (PMF) annual update, in conjunction with the CHMP Epidemiological guideline,
- 2006 and 2007 PMF evaluation reports for the relevant PMF

Feedback on this work was provided to the PMF Drafting Group and to BWP/CHMP and a revision of the guideline was recommended.

1. INTRODUCTION (background)

The CHMP/BWP assigned to the Epidemiological expert group the task of conducting an extensive critical analysis of the data in the PMF dossiers, and a revision to the guideline is aimed to improve the PMF dossiers with better submission of data and consistency across evaluations.

The revision will contribute to the harmonised understanding of the PMF data submission and reporting to the EMEA for the PMF initial certification and subsequent annual updates. This will be of benefit to both PMF stakeholders and PMF coordinators/assessors.

2. SCOPE

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

- Submission of Epidemiological data
- Reporting critical analysis of Epidemiological data (e.g. identification and reporting of trends)
- residual risk estimations and elements to be considered for the calculations

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 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. MAIN GUIDELINE TEXT

1. 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. The purpose of collecting these data is to characterise the donor population with respect to infection risk, to allow trend analyses to be undertaken over periods of time, and to allow comparison of risks between donor populations of individual collection centres. 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 transfusion transmissible infectious markers in donors and the estimated risk of infectious donations entering the plasma supply should be presented and discussed according to the present guidance.

Continuous epidemiological evaluation at individual blood/plasma collection centres together with an annual update of the assessment are therefore required.
This guideline will be kept under review in the light of experience with its use and any future EU requirements and guidance relevant to its content.

2. 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 underly 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 HBsAg test results, while the Plasma Master File (PMF) holder should also report separately the results of additional screening tests (e.g. NAT assays or anti-HBc). 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 definitions [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.
Since no confirmatory assay designed for anti-HBc exists, PMF Holders may report repeat reactives for this marker. When a complementary test is applied it should be indicated.

Further practical details for reporting data are set out in Section 5.

3. 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[a] 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**[b]:

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.

4. 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 and plasma donors.
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

[a] 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.

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

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.

Prevalence in the context of the study of a donor population can be defined as **(formula 1)**:

$$\frac{\text{No. of positive donors in a specified period}}{\text{Total No. donors in the same specified period}}$$

This is often expressed per 100,000 donors. 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 5).

Incidence in the context of the study of a donor population can be measured in "repeat tested donors" as **(formula 2)**:

$$\frac{\text{No. of donors who had a negative test result followed by a positive test result in the study period}}{\text{The sum of the time between the first and the last test result of every donor during the study period/365 (= person-years)}}$$

This is often expressed per 100,000 person-years. In the case of HBsAg an adjustment is needed to get an estimation of true incidence where donation is infrequent as an HBsAg positive may be missed (see also 7.1).

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.

An alternative approach to **estimate** incidence is as **(formula 3)**:

$$\frac{\text{No. of positive repeat tested donors in the study period with a previous negative donation}}{\text{The total No. of donations from repeat donors in the study period x mean interdonation(*) interval (expressed in years)}}$$

(*) Interdonation interval derived from counts of donations and donors.

Important note: *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).*

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[8].

5. RECOMMENDATIONS FOR REPORTING OF DATA ON INFECTIOUS DISEASE MARKERS

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 2 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 (see section 7 below), collection centres should report the number of donations collected as well.
Data should be reported using the tabular formats given in Tables 1 and 2 in the Appendix, per country, per organisation and per centre. If within a country both blood banks and plasma source centres are used for the collection of blood/plasma, data for this country should also be summarised separately for each of these two categories. The data should be reported for the calendar year (January – December). In order to facilitate a relative assessment of these data, the data should be presented in absolute numbers and calculated per 100,000 donors.

5.1 "First time tested donor" population

According to the definition in Section 3, "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[c], 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:

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

5.2 "Repeat tested donor" population

As described in Section 3, 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".

[c] **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.

Rate of positive "repeat tested donors" in a given period[d]

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

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).*

6. EPIDEMIOLOGICAL ASSESSMENT OF DONOR POPULATIONS, AND TRENDS OVER TIME

The criteria used by the PMF Holder to establish acceptable ranges for epidemiological data, and to identify any individual blood/plasma collection centres reporting data above the acceptable range, should be described. The results of the analysis should be provided and information given on any collection centres outside of the acceptable range and the corrective actions taken.
A comparison should be made with the data provided over the three previous years of reporting for the individual collection centres, organisations and countries. A table summarising the epidemiological data per organisation and country as well as per type of collection system over the three previous years of reporting should be provided and any significant trend in data discussed. Significant trends in individual collection centres should be discussed as well, highlighting centres exceeding the acceptable range. The purpose is to identify any overall trends in the rates of infectious markers in the donor population. In addition, the effectiveness of remedial actions for collection centres, which have previously been identified as above the acceptable range, should be discussed.
Any trend observed in the results of additional screening tests (e.g. NAT assays or anti-HBc) should be included in the assessment and discussed.
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.
If formal epidemiological studies have been carried out in the donor population, the results should be provided including information on the methodology used, and trends over time discussed. An example of tests to detect trends has been published[8].

7. ESTIMATION OF THE RISK OF INFECTIOUS DONATIONS PASSING UNDETECTED THROUGH ROUTINE DONATION SCREENING

7.1 Recommended method for estimation of risk

Introduction/general

The method used by the PMF Holder to estimate the risk of infectious donations passing undetected through routine testing at the time of donation collection should be fully described. Citing a reference describing the method is not sufficient. Details should be included that enable the calculations to be reproduced by a reader of the PMF. This section includes recommendations on how to present the different elements necessary to estimate this risk and describes a method for calculation of risk estimates based on those elements.

If PMF holders use this method, then reporting of the details in Table 3 in the Appendix should suffice to describe their calculations. If PMF holders use an altered version of the standard method, or a different

[d] 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

method, this should be fully described and justified. The results of risk estimate should be reported using the tabular format in Table 4 in the Appendix.

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.

The application of risk-reduction measures to the plasma supply post-single donation screening, including inventory hold, look-backs, or further NAT testing of manufacturing plasma pools is not to be included in the risk estimate reported to the EMEA (in Table 4). These additional risk reduction measures and their impact on risk 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) EMEA/CPMP/BWP/125/04.

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, and
- 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 4):**

Risk = ((1-sensitivity)x(prevalence/sensitivity)) + (error rate x prevalence) - (((1-sensitivity) x (prevalence/ sensitivity)) x (error rate x 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 risk of passing '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.

Methods

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

As a standard method, PMF holders are advised to use the basic "incidence" method[4, 10] to estimate this risk of an infectious donation being undetected by all routine testing performed prior to the release of donations to storage and/or pooling. This is referred to throughout this document as the "window period" risk.

-Window period risk calculation in repeat tested donors (formula 5):

Window period risk for infection Y	=	incidence of Y	x	infectious window period of routine tests for Y (expressed in years)

Where, *incidence* in "repeat tested donors" is calculated using formula 2, as in Schreiber *et al*[4, 7], or alternatively is estimated using formula 3).

And where, the *infectious window period* is a justified estimate of this time period for the testing applied. If more than 1 test is routinely applied to all donations, e.g. anti-HCV and HCV NAT, the shorter window period should be used. There is generally some uncertainty in the length of the infectious window period, and the value chosen should be justified. It is recommended that PMF holders use a mid-point or median value where there is a range, unless another value is justified.

Typically, the length of the window period for NAT is shorter than for serological testing: hence the reduction in risk that is generally expected and achieved by NAT.

Incidence is typically expressed per 100,000 person years, and the window period should also be measured in years. The resulting risk estimate is then expressed per 100,000 donations. It is however common and advisable to report the risk per million donations (i.e. to multiply risk per 100,000 donations by 10 for standardised reporting purposes, as specified in Table 4).

The "incidence" method can mis-estimate (overestimate or underestimate) the "window period risk" in some circumstances if the interdonation interval of donors who acquire new infections is significantly different (longer or shorter) than the interdonation interval for all other donors. Rather than including a further calculation stage to adjust for this, PMF holders are requested to report the average interdonation intervals for their a) "repeat tested donors" who acquire a new infection, and b) all "repeat tested donors", and to comment on the likely over- or under-estimation of risk if these intervals differ markedly (i.e. by ~20% or more).

- The "new donor incidence adjustment factor"

Incidence in "first time tested donors" should be estimated from either a) the rate of NAT-positive-only donations amongst donations from "first time tested" donors or b) the incidence in "repeat tested donors" multiplied by a factor that represents the relative risk of new infections amongst "first time" donors compared to "repeat" donors. This "new donor incidence adjustment factor" should be based on a justified, local measure of the risk of new infection in "first time tested donors". The simplest recommended method to do this, where testing and data allow, is to calculate the relative frequency of NAT-positive-only donations from "first time" and "repeat" donors. Where NAT is not used for an infection, or is used but yields very low numbers of NAT-positive-only donations (i.e. less than 5 in either "first-time" or "repeat" donors during the time-period under review, as may often be the case for example for HBV NAT), or may pick-up non-acute infection (e.g. HBV carriers with undetectable HBsAg) another method to estimate the "new donor incidence adjustment factor" should be described and used. Possible approaches include: the relative prevalence of an infection during the first 3-6 months of testing "first time" and "repeat" donors for an infection when the prevalence in both groups of donors is an equivalent measure of cumulative incidence[11]; the relative frequency of donations found positive for other markers of 'acute' infection (e.g. IgM for HBV) from "first time" and "repeat" donors, or by deriving annual incidence amongst "first time tested donors" from the prevalence (i.e. cumulative incidence) divided by the (assumed) time at risk[12]. Other methods of estimating the "new donor incidence adjustment factor" may be acceptable. The method chosen should be explained within the PMF in sufficient detail for the calculations to be reproduced without access to references.

- The HBsAg adjustment factor

PMF holders who use observations of seroconversion for HBsAg as the numerator in their HBV incidence calculations (see Section 4) must explain how they have adjusted for the transient nature of HBsAg, i.e. for the probability that a new HBV infection in a "repeat tested donor" may have resolved their infection and be HBsAg negative by the time of their first donation after acquiring HBV infection.

The value of this adjustment factor depends on a) the duration of HBsAg amongst HBV infected adults and b) the interdonation interval. The value of a) is probably the same in most populations and may be taken from the literature[13, 14, 15, 16, 17]. The value of b) must be true/justified for the PMF's donor population, i.e. can not be taken from the literature or data about other plasma collection systems and must be based on the donor population that is the subject of the PMF.

Taking the assumptions as used by Korelitz et al[13], who assumed that 70% of infected donors would have transient antigenaemia lasting an average of 77 days (duration of HBsAg detection was modified by Seed *et al* to add 14 days to the delay of 63 days adopted by Korelitz to take into account the better sensitivity of

current HBsAg assays), that 25% of infected donors would have no antigenaemia and that 5% would have persistent antigenaemia, this calculation is as follows (formula 6):

HBsAg adjustment (i.e. probability of detection by HBsAg testing) = (5%x1) + (70%x (77/IDI))

Where IDI = the average interdonation interval for donors who seroconverted for HBsAg, i.e. days between last HBsAg-negative donations and first HBsAg-positive donation.

7.2 Reporting of risk estimates

Results should be reported using the tabular format given in Tables 4 in the Appendix. Estimates (and their component parameter values) must be reported by calendar year, per million donations, separately for:

- Each of these infections: HBV, HCV & HIV
- Donations from a) "repeat tested donors" and, where donations from "first time tested donors" are used for plasma product production, from b) "first time tested donors" and for all donations based on combined risks for a) and b) weighted by contribution according to percentage by donations collected.
- Each large, distinct geographical region and, when applicable, organisation of donation collection, i.e. each country, organisation and – where regions of a country e.g. states within USA, may have distinct epidemiology – each large collection sub-region.
- If risk varies significantly within the categories above, because, for example, tests with different window periods (or mini-pool sizes) are used, or there are different donation collection practices such as whole blood vs plasmapheresis, a worst case situation (i.e. longest window period, shortest interdonation interval) should be calculated and presented at a minimum, AND OPTIONALLY risks may be calculated and presented for each alternative (lower risk) system.

7.3 Further developments

Interpretation of the risk estimates requires understanding of the range of uncertainty around the point estimate.

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