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Committee for Medicinal Products for Human Use (CHMP)

Chapter 9 of Guideline on epidemiological data on blood transmissible infections

Draft

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Note:

This revision is only revising chapter 9 of the full guideline: Guideline for epidemiological data on blood transmissible infections Upon finalisation the chapter 9 will be merged in the full guideline.

Comments should be provided using this EUSurvey form. For any technical issues, please contact the EUSurvey Support.

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Guideline on epidemiological data on blood transmissible infections

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Executive summary

The revision of this guideline follows an earlier revision of this guideline (EMA/CHMP/BWP/548524/2008. Rev 1) which came into effect in 2016.

In 2023, in view of the experience gathered during the review of the Alert Limits information in recent PMF annual updates (AU) and the requests from the plasma fractionation industry for further guidance, the need to expand the information for PMF holders on the approach and the statistical method for the appropriate calculation of alert limits was identified. The revision and expansion on the Alert Limit calculations of the epidemiological guideline is proposed as part of the 3-year BWP workplan 2024-2026.

1. Introduction (background)

The present document represents a revision of the chapter 9 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

This revision concerns the requirements for the Alert Limits that are used to evaluate epidemiological data. Additional guidance on suitable statistical models that could be used in the definition of Alert Limits was published in an EMA Q&A (EMA/CHMP/BWP/721411/2022). However, experience accumulated in recent years of PMF evaluation reveals that a more detailed guidance for PMF holders needs to be provided on the calculation of Alert Limits, which impacts on the information to be submitted in the dossier. This revision of the guideline will provide guidance in the following aspects:

- Definition of Alert Limits by type of donor (first time tested/repeat tested donors), recovered/source plasma centres and and geographical area;
- Data set on viral marker rates, and time period used for the establishment of the Alert Limits;
- Criteria for periodic review/recalculation of Alert Limits;
- Cut-off levels for each viral marker that allows the identification of outlying centres;
- Statistical model to calculate Alert Limits;
- Data to be submitted by PMF holders regarding Alert Limits necessary for regulatory assessment.

3. Legal basis

[..]

4. Purpose

[..]

5. Infectious disease markers

[..]

6. Donor classifications

[..]

7. Prevalence and incidence

[..]

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

[..]

8.1. "First time tested donor" population

[..]

8.2. "Repeat tested donor" population

[..]

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.

Monitoring change

[..]

Alert Limits

Donor selection requirements are an important part of the measures taken to reduce the risk for transmission of blood transmissible agents by plasma-derived medicinal products, in addition to testing of donations and plasma pools, and virus reduction during manufacture. Assessment of epidemiological data is considered as one of the essential tools to ensure that donors with a high risk of being infected with blood transmissible agents are excluded from donation. If the donor population of a blood/plasma collection centre has a considerably higher infection rate for one or more viral markers (HIV, HBV, HCV) in comparison to similar donor populations of other blood/plasma collection centres included in the PMF, this could indicate that its donor selection procedure does not sufficiently exclude high-risk donors and corrective actions are needed or the collection centre is not optimally located to exclude high-risk donors. To identify such collection centres, the PMF holder should define Alert Limits.

Considering the purpose of the Alert Limits, they should be based on the epidemiological data of the donor population in the respective PMF and sufficient granularity should be applied:

- The infection rate usually differs greatly between HIV, HBV and HCV infections, therefore Alert Limits should be defined separately for HIV, HBV and HCV.
- Epidemiological data from "first time tested (FTT) donors" and "repeat tested (RT) donors" should be interpreted in a different way in the context of infection control. Whereas Alert Limits for FTT donors will have a function of setting criteria for anomalies with regards to prevalence (potentially associated with incidence), Alert Limits for RT donors will serve the primary purpose of identifying outliers of incidence. Therefore, separate Alert Limits should be set for FTT donors and RT donors. Alert Limits for both FTT donors and RT donors are expected even if plasma from FTT donors is not used for fractionation, as both Alert Limits are considered of importance for the evaluation of the epidemiological data of collection centres.
- Separate Alert Limits should be defined for collection centres in different geographical regions. At a minimum, separate limits are required for Europe, for North America (USA and Canada) and for other countries outside Europe, as it is known that the infection rates in these regions may differ substantially. It may be necessary to further differentiate Alert Limits for collection centres in groups of countries or American states to ensure that the Alert Limits are sufficiently sensitive. The required level of differentiation will depend on the collection centres that are included in the PMF. The chosen approach should be justified based on epidemiological data of the collection centres.
- In some geographical regions the infection rates for recovered plasma donors and source plasma donors show substantial differences. If both source and recovered plasma are collected in a geographical region, separate Alert Limits should therefore be defined for centres collecting source plasma and centres collecting recovered plasma, unless the use of the same Alert Limits can be justified based on e.g. comparable epidemiological data, difficulties in separating the data, or a limited number of source or recovered plasma donors.

As a consequence, the calculations and evaluation described in the following sections, should be performed for each virus type, donor type, geographical region and plasma type.

Calculation and reporting of Alert Limits

To harmonize the evaluation of epidemiological data, the Alert Limits should be calculated using the 95th percentile method, as defined below. The Alert Limits should be defined as a maximum allowed number of positives per 100,000 donors.

The epidemiological data of all collection centres included in the PMF in any time period during the most recent five years should be used for the calculation. To avoid having a large number of zero's in the data set, which would complicate the interpretation of infection rates, the total number of positive donors and the total number of donors over five years of the individual collection centres should be computed. The unit of infection rate, for each collection centre, is then defined as follows:

$$\frac{total\ number\ of\ positive\ donors}{total\ number\ of\ donors} \times 100{,}000$$

The 95th percentile of the collection centres included in the respective calculation is defined as the Alert Limit for the PMF holder.

All Alert Limits should be presented using the tabular overview provided in the Appendices to the Guideline (Table 5).

Evaluation of epidemiological data using Alert Limits and reporting of results

At the time of each Annual Update the epidemiological data of the collection centres included in the PMF should be compared with the Alert Limits. All collection centres with infection rates exceeding the applicable Alert Limit(s) should be reported per the tabular overviews in the Appendices to the Guideline.

Collection centres exceeding the applicable Alert Limit having only 1 positive donor do not need to be listed individually, because the occurrence of 1 positive donor could be a chance finding and these findings have to be interpreted with caution. For completeness, the number of these collection centres should be reported using Table 6.

Collection centres exceeding the applicable Alert Limit **and** having more than 1 positive donor for the respective viral marker should be reported using Listing 1 and 2. The potential reasons for exceeding the Alert Limits at these collection centres should be evaluated and discussed, considering e.g. the actual number of positive donors, the available data from previous years and any trends in infection rates. Based on this evaluation it should be determined if corrective actions and/or further monitoring is needed. The individual collection centre control chart may be included as part of the discussion.

Corrective actions should be taken in case the epidemiological data indicate that donor selection may need to be improved. These corrective actions should be briefly described and should be aimed at improving the donor selection procedure or other identified problems and thereby reduce the infection rates. It may be required to provide more recent epidemiological data to demonstrate the corrective actions were effective and the situation has improved. In some cases, the use of plasma from FTT donors or the respective collection centre may be refused until obvious improvement has been demonstrated.

When the addition of new collection centres is applied for, the epidemiological data of these collection centres should be compared to the Alert Limits as described above. If the Alert Limits are not suitable for this purpose, additional Alert Limits should be defined. This might be needed if:

- the collection centres are located in a geographical area that was not previously represented in the PMF, or
- the collection centres represent the first supplier of source or recovered plasma in the PMF.

In other cases, introduction of separate Alert Limits for new collection centres can only be accepted, if the need is driven by differences in infection rates in the general population and not by differences in donor selection.
The approach chosen to compare the epidemiological data of new collection centres to Alert Limits should be justified.

Update of Alert Limits:

Update of Alert Limits should be performed every 5 years using the epidemiological data from collection centres included in the PMF in the most recent 5 years and using the percentile method described above. The updated limits should replace the previous Alert Limits.

If the update results in an increase of the Alert Limit(s), this should be justified. Unless the increase is minor, the reasons for the increase should be evaluated and, if needed, corrective actions taken. If Alert Limits increased due to changes in the geographical regions from which plasma is collected, introduction of separate Alert Limits for different geographical regions should be considered.

Table 5 Alert Limits								
Region	**Plasma Type**	**Data collection[4]**	**Alert Limit per 100,000 donors**					
			HIV, FTT	**HIV, RT**	**HCV, FTT**	**HCV, RT**	**HBV, FTT**	**HBV, RT**
Europe[1]	Source							
Europe[1]	Recovered							
North America[2]	Source							
North America[2]	Recovered							
…[3]								

1 Include further granularity (i.e. Alert Limits for different groups of European countries) if needed

2 Include further granularity (i.e. Alert Limits for different groups of American states or for USA and Canada) if needed

3 Include additional regions if needed

4 Indicate the years from which the epidemiological data were used to calculate the Alert Limit

Table 6 Number and percentage of collection centres with infection rate above the Alert Limit that have only 1 positive donor							
Region	**Plasma Type**	**HIV, FTT**	**HIV, RT**	**HCV, FTT**	**HCV, RT**	**HBV, FTT**	**HBV, RT**
Europe[1]	Source	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Europe[1]	Recovered	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
North America[2]	Source	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
North America[2]	Recovered	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
…[3]							

1 Include further granularity (i.e. Alert Limits for different groups of European countries) if needed

2 Include further granularity (i.e. Alert Limits for different groups of American states or for USA and Canada) if needed

3 Include additional regions if needed

Listing 1 Source plasma collection centres with infection rate above the Alert Limit and having ≥ 2 positive donors						
Country	**Centre ID**	**Centre name**	**Total number of donors**	**Infection rate per 100,000 donors**	**Number of donors tested positive**	**Allowed number of donors tested positive[1]**
FTT donors, HIV						
…						
RT donors, HIV						
…						
FTT donors, HCV						
…						
RT donors, HCV						
…						
FTT donors, HBV						
…						
RT donors, HBV						
…						

1 Indicate the maximum number of positive donors that is possible for the number of donors in a centre without exceeding the Alert Level

Listing 2 Recovered plasma collection centres with infection rate above the Alert Limit and having ≥ 2 positive donors						
Country	**Centre ID**	**Centre name**	**Total number of donors**	**Infection rate per 100,000 donors**	**Number of donors tested positive**	**Allowed number of donors tested positive[1]**
FTT donors, HIV						
…						
RT donors, HIV						
…						
FTT donors, HCV						
…						
RT donors, HCV						
…						
FTT donors, HBV						
…						
RT donors, HBV						
…						

1 Indicate the maximum number of positive donors that is possible for the number of donors in a centre without exceeding the Alert Level

10. Residual risk: Risk estimation of undetected viraemic donations in routine testing

[..]

11. Reporting and interpretation of "worst case" estimates of the "window period risk"

[..]

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

[..]

References

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