EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on revision of Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008)

Agreed by Biologics Working Party	June 2014
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Start of public consultation	1 August 2014
End of consultation (deadline for comments)	31 December 2014

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

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1. Introduction

The guideline on epidemiological data on blood transmissible infections (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.

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

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.

The goal is final product safety and this is based on complementary approaches to assure virus safety (e.g. donor selection/donation testing, and virus reduction by the production process).

The first revision of this guideline came into effect in 2011, and it was recognised at that time that a further revision may be needed based on the experience of data submission and evaluation.

2. Problem statement

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.

One of the important parts of the PMF is an understanding of the epidemiology of virus infections in the donor population. Currently, a variety of approaches are being used to monitor trends and to establish acceptable ranges for epidemiological data. PMF evaluation reports currently state that no final decision on the acceptability of these different approaches will be taken until further evaluation of the approaches by the PMF epidemiology group.

A PMF epidemiology expert group meeting took place in December 2013 to look at these approaches and the general experience with the guideline. A number of issues have been identified where additional guidance to PMF holders may be needed by means of the revision of the Guideline, in particular:

- Residual risk calculation - HBsAg adjustment factor, 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 both graphical representations of trends and statistical significance approaches for trend analysis for organisations/countries

- Approaches to identify trends on a centre basis

- Criteria for acceptance of new centres in terms of epidemiological data.

A further epidemiology meeting with industry is now scheduled to take place in November 2014 to discuss the topics highlighted above. The concept paper consultation period has been aligned to allow stakeholders to provide their comments after the November meeting.

3. Discussion (on the problem statement)

Alert limits and trend analysis:

Alert limits are useful to identify collection centres that perform worse than expected when compared to similar collection centres, i.e. as a quality control system.

As such, it is reasonable that PMF holders define their own alert levels and if a centre is identified that performs worse than expected, corrective actions should be taken and reported in the PMF.

In addition, a comparison across countries/organisations can identify a country/organisation with particularly high incidence/prevalence. At present it is not possible to define a “universal” incidence or prevalence rate that could be used as an upper limit for acceptance of plasma.

Trend analysis goes hand-in-hand with alert limits and the current guideline recommends that this is done at the level of individual collection centres, organisations and countries. Trend analysis can help to identify when a particular centre/organisation/country has an issue with epidemiology and also the effectiveness of corrective and preventive actions.

The usefulness of graphs demonstrating trends on a country/organisation basis to differentiate a consistent trend from random fluctuations will be considered, as well as the reporting of statistical significance of trends.

Data in the guideline format is now available for periods longer than the 4 years specified in the current guidance. Trend analysis over longer periods can help to distinguish between trends and random fluctuations.

Residual Risk (RR)

Based on the experience gathered from the PMF evaluations, it is considered that further guidance on this aspect may be helpful. As stated in the guideline, the purpose of the risk estimate is to represent a reasonable ‘worst case’ situation. The RR calculation for the worst case scenario is important, but is only a part of the epidemiological assessment; the “raw unmodified” epidemiological data are also important.

This RR calculation approach may be used as a consistent tool to calculate potential pool contamination also for “new viruses” for which infection rates, length of viraemic phase and viral concentration in this phase are known.

The guideline revision will consider whether additional guidance is helpful in order to have the calculations for the different PMFs in a more uniform way and further define factors which have the most impact in the calculation (e.g. window days and HBsAg adjustment factor).

The revision will also consider how to deal with the situation where there are no positive reported cases to be included in the residual risk assessment (e.g. by extending the time period of epidemiological data used in the calculation beyond one year).

When to accept new centres with limited epidemiology data

The revision also proposes to address “How to deal with new centres and what epidemiological data is needed”. This question requires a case-by-case decision taking account of the situation (e.g. new centre for organisation already in PMF, new organisation or county of collection) and the available epidemiological data. For new centres relating to a new organisation for the PMF, a minimum amount of epidemiological data may be required.

4. Recommendation

The Biologics Working Party (BWP) recommends revising the Note for Guidance (CHMP/BWP/548524/08).

A workshop with industry and PMF/epidemiology experts is intended to take place in November 2014 to discuss the issues highlighted in this concept paper. The outcome of the meeting and comments received on this Concept paper will be the basis for preparing a revision of the Note for Guidance.

Focus will be on providing additional guidance on residual risk calculation, trend analysis and alert limits, and criteria for acceptance of new centres.

5. Proposed timetable

Further to the industry meeting and the consultation period in 2014, this guideline will be discussed during the meetings of the BWP in 2015. It is anticipated that a draft revised guideline will be released for external consultation during 2015.

6. Resource requirements for preparation

There will be one Rapporteur involved in the preparation of the guideline. The draft will be discussed with the PMF and Epidemiology drafting groups as well as with the BWP.

7. Impact assessment (anticipated)

The revised guideline will reflect the experience gained from the submission and evaluation of epidemiological data as part of the PMF certification process. A particular aim of this revision is to provide guidance on suitable approaches for setting alert limits and monitoring trends. It aims to set clear standards and expectations for Industry in the areas where there are remaining questions. The overall impact of this guidance is to provide reassurance about the epidemiological situation in blood centres, and to identify collection centres that perform worse than expected when compared to similar collection centres, i.e. as a quality control system.

The resource implications for revision of the guidelines are considered justified by the fact that application of updated guidance will further clarify requirements for PMF holders and regulators and should result in less resources being needed during the PMF evaluation.

8. Interested parties

Interested parties with specific interest in this topic will be consulted during the revision of this guideline, including:

- IPFA, PPTA, and PMF-holders/applicants
- European Commission and EDQM
- Within the European Medicines Agency, there will be consultation with the PMF drafting group, PMF Epidemiology core group, Biologics Working Party and CHMP.

9. References to literature, guidelines, etc.

1. Guideline on epidemiological data on blood transmissible infections (EMA/CHMP/BWP/548524/2008)

2. PMF dossiers evaluations