European Medicines Agency
*Evaluation of Medicines for Human Use*

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# COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

# GUIDELINE ON ASSESSING THE RISK FOR VIRUS TRANSMISSION – NEW CHAPTER 6 OF THE NOTE FOR GUIDANCE ON PLASMA-DERIVED MEDICINAL PRODUCTS (CPMP/BWP/269/95)

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**Note:**
This risk assessment guideline comes into immediate operation for the purpose of supporting the warning statements specified in the Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for Plasma-derived Medicinal Products (CPMP/BPWG/BWP/561/03). Other recommendations come into operation by the end of April 2005.

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NOTE FOR GUIDANCE ON ASSESSING THE RISK FOR VIRUS TRANSMISSION – NEW CHAPTER 6 OF THE NOTE FOR GUIDANCE ON PLASMA-DERIVED MEDICINAL PRODUCTS (CPMP/BWP/269/95)

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## 1. INTRODUCTION

The aim of this chapter is to outline the general principles that manufacturers should follow in performing risk assessments for virus transmission by plasma-derived medicinal products. These risk assessments are required for the substantiation of statements on virus safety and any remaining potential risk in the product information for these products, as outlined in the Note for Guidance on the Warning on Transmissible Agents in SPCs and Package Leaflets for Plasma-derived Medicinal Products (CPMP/BPWG/BWP/561/03). The risk assessment should, where possible, include a quantitative estimation of the probability of a virus contaminant being present in a defined dose of final product. The principles presented below can be applied to both known and emerging viruses.

## 2. GENERAL PRINCIPLE OF THE RISK ASSESSMENT

The principle of the risk assessment is to consider various factors, such as epidemiology, viraemic titre, testing for viral markers, virus inactivation/removal steps and product yield, that influence the potential level of infectious virus particles in a dose of final product. The reliability of the risk assessment will depend on the extent of information available on these factors. Many of the factors may vary and realistic worst case scenarios should be considered in order to obtain a result which can give greatest assurance for the statements on viral safety.

An estimate of the capacity of the manufacturing process to inactivate or remove the contaminant virus ("overall virus inactivation/removal capacity") versus the potential amount of a given virus that may be present in the starting material ("potential virus input") should also be provided. In addition, by considering the amount of starting material needed to manufacture a single dose of product, the probability of potential virus contamination in a single dose of the final product can be estimated.

### 2.1 Potential virus input

For viruses that are potential contaminants of human plasma, the amount of virus that may contaminate the plasma pool for manufacture ('potential virus input') should be estimated. The 'potential virus input' is determined by the number of viraemic donations that could enter the manufacturing pool, the volume of individual donations and the titre of a viraemic donation that might escape detection in a virus assay.

The number of viraemic donations depends on the epidemiology in the donor population and on the frequency of donations from an individual donor. Donor selection and exclusion criteria, as well as inventory hold measures, should be assessed for their effectiveness in decreasing the number of viraemic donations that may enter the manufacturing pool. Any available information on the specific donor population from the Plasma Master File should be incorporated into the risk assessment. In cases where such data are not available, information should be sought from other sources e.g. general epidemiological surveys or investigational studies on the donor population.

The viraemic period should be described with respect to its length and virus titre. With respect to individual screening by specific tests (serological or nucleic acid amplification technologies (NAT)), the titre of viraemic donations that are not recognised by such tests (e.g. donations from the 'window period') has to be considered. A 'minipool' represents a defined number of aliquots of donations that are pooled for testing purposes. Testing of minipools (e.g. by NAT) may be a valuable tool in identifying and excluding highly viraemic donations. In both cases, single donation testing and minipool testing, the 'potential virus input' in the manufacturing pool has to be extrapolated using estimates on the titer and on the number of undetected viraemic donations. Measures that identify and exclude contaminations at the

minipool level or at the single donation level will more readily detect a contamination than tests applied to the manufacturing pool. However, a sensitive NAT testing of the manufacturing pool defines a well-controlled upper limit for a potential virus contamination.

### 2.2 Virus inactivation/removal capacity

The principles for determination of the virus inactivating/removal capacity of a production process and for interpretation of these data have been outlined in the CPMP guideline on virus validation (CPMP/BWP/268/95). Virus validation is an approach that has to be interpreted carefully, considering qualitative aspects in addition to quantitative data. For example, the reliability of the data from scaled-down experiments and of the virus reduction factors with respect to variations of manufacturing process parameters, should be carefully considered. Other limitations include the validity of summing-up logarithmic reduction numbers from single steps, the relevance of the viruses used in validation studies (model viruses or specific laboratory strains from the same species), and experimental limitations on the level of inactivation/removal that can be measured.

For emerging viruses, the specific physical characteristics of the emerging virus should be discussed carefully with respect to any model viruses for which data have previously been derived. If it is possible to handle the emerging virus in the laboratory, investigational studies are recommended to evaluate the relevance of previously derived data. If it is not possible to use the emerging virus for investigational studies, and if pre-existing data were derived using viral species that are not adequate models of the emerging virus, investigational studies with a closely related model virus should be considered. Depending on the available data, further validation with the relevant virus or a more specific model virus should be decided on a product-specific basis.

### 2.3 Contribution from specific antibodies to virus safety

Specific antibodies may contribute to virus safety. A specification of the antibody content in the final product and validation of its neutralisation capacity could substantiate the role of specific antibodies in assuring the virus safety of a specific product. The benefit of specific antibodies in the pool for fractionation is difficult to assess as there is no reliable information on viral neutralisation at this manufacturing stage nor on the stability of virus-antibody complexes during further downstream processing. If claims are made in the risk assessment on removal of virus-antibody complexes from product intermediates, this should be substantiated by appropriate validation data.

### 2.4 Estimation of virus particles in the finished product

As a general principle for a safe product, the virus inactivation/removal capacity should clearly exceed the potential amount of virus that could enter the production process leading to an adequate safety margin of the finished product. However, no specific limit is defined because, as outlined above, the viral reduction factor is subject to various qualitative aspects of interpretation and the potential number of viral particles per vial of product should be discussed in relationship to these and other factors.

The amount of plasma used for production of one vial of final product should be defined considering the product yield from plasma, the batch size, and the number of vials produced from a batch. The relevant data should be provided from process validation. The information on the amount of required plasma should be used along with the data deriving from virus validation studies and the potential viral input to estimate the number of viral particles per vial. The estimated number of viral particles per vial can be calculated from the product of

the worst case virus concentration in the starting material and the plasma required to produce one vial, divided by the viral reduction factor obtained from validation studies.[1]

The number of estimated virus particles per vial may also be discussed in respect to what is known about the minimum human infectious dose and the amount of medicinal product typically used in treatment. Any statement about the human infectious dose should be substantiated by data regarding the route of administration. If such data are not available, a conservative approach using viral genomes as an indicator of potentially infectious virus particles in the starting material should be followed. In-vitro infectivity data is generally not acceptable.[2]

### 2.5 Clinical experience and surveillance

The clinical experience with respect to virus transmission from the product, including any reports of virus transmission with the product or any similar product, should be discussed. It should be borne in mind that virus transmissions tend to be related to specific batches of product. The number of investigated patients from clinical studies is usually too low to detect infections, and only a limited number of batches are used. A long and satisfactory clinical experience may be very helpful to support the safety of a product, provided that any factor affecting virus safety (e.g. epidemiology) is not significantly changed. However, an absence of reported transmissions does not prove the viral safety of a product e.g. because undetected transmissions may have occurred or the product may have been used in a non-susceptible population. This is especially the case for emerging viruses or viruses that have not been carefully considered by a surveillance system (such as B19 virus).

## 3. APPLICATION OF THIS GUIDELINE

A viral risk assessment for HIV, HBV, HCV, B19 and HAV should be performed for all new marketing applications with the exception of albumin (see below). This will substantiate statements on virus safety and any remaining potential risk in the SPC, as outlined in the Note for Guidance on the Warning on transmissible agents in SPCs and Package Leaflets for plasma-derived medicinal products (CPMP/BPWG/BWP/561/03).

For products for which a marketing authorisation has already been obtained, a risk assessment will be expected for HAV and B19 if claims are made regarding effective measures for these viruses. If no claims are made, no risk assessment is required. In either case, risk assessments for HIV, HBV and HCV are not required.

A risk assessment will not be expected for new marketing applications or existing marketing authorisations in the case of albumins manufactured according to European Pharmacopoeia specifications and by established fractionation processes. For such albumins, a general statement on virus safety is foreseen in the core SPC. A risk assessment would be expected if an albumin was manufactured by other methods.

According to Section 2.3.6 of Guideline CPMP/BWP/269/95, the relevant Medicines Competent Authority(ies) have to be informed when there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A, B, or C. A lot-specific risk assessment should be performed whenever post-pooling information indicates that a

[1] $N = c \times V \div R$ where N is the potential number of viral particles per vial of product, c is the potential virus concentration in the plasma pool, V is the volume of plasma required to produce one vial of product, R is the viral reduction factor obtained from validation studies. An example of this type of calculation is given in ICH guideline Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin (CPMP/ICH/295/95).

[2] It is usually not clear if the relation between infectious particles and genomes from a virus which has been produced in cell culture reflects the virus which occurs *in vivo*. Further, the sensitivity of the cell culture system may not reflect the efficiency of an *in vivo* transmission event.

contaminated donation has entered the manufacturing plasma pool[3]. In such situations, reference can be made to the risk assessment included in the Marketing Authorisation Dossier. A specified NAT limit of the manufacturing pool may be helpful in substantiating such risk assessments.

[3] Further guidance on the actions to be taken in this situation is provided in this Note for Guidance on Plasma-derived medicinal products in the section on source materials, and in Annex 14 to the EU guide to Good Manufacturing Practice.