الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guideline on Blood Products
Plasma Derived Medicinal Products

Version 1.1

Date of issue	22/08/17
Date of implementation	22/08/17

بالأهــــــم نهتــــــم

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Saudi Food & Drug Authority

Drug Sector

For Inquiries   *sdr.drug@sfda.gov.sa*

For Comments   *Drug.Comments@sfda.gov.sa*

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

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Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

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Document Control

Version	Author	Date	Comments
1.0	Executive Directorate of Products Evaluation	22/08/17	This guideline replaces "Guidelines for production and quality control of blood product (Version 1.1)"
1.1	Executive Directorate of Regulatory Affairs	09 November 2022	This version doesn't include any scientific update

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EXECUTIVE SUMMARY

This guideline provides guidance for the collection and control of starting material (human plasma), the manufacturing process, the quality control, stability studies, adventurous agents studies of blood products. The guideline gives specific attention to the virus safety of medicinal products that are derived from human plasma. It although addresses and highlights points to consider for each specific class of blood products. This guideline applicable for:

- Medicinal products with human plasma-derived proteins as active substances. Investigational medicinal products with plasma proteins as active substances.
- Human Plasma derived proteins used as excipients in medicinal product, including investigational medicinal products.

1. INTRODUCTION (BACKGROUND)

Human plasma contains many proteins which, following extraction, purification, and formulation into medicinal products are of great medical importance. Plasma-derived products provide life-saving therapies but the number of donors limits the quantity of plasma for fractionation. Therefore, the exchange of intermediates between manufacturers or the use of a variant manufacturing process (see below) may be possible to assure the best use of blood/plasma donations.

Although the therapeutic use of blood transfusion goes back to the beginning of the 20th century, it was not until the 1940s that the technique of plasma fractionation, devised by Cohn and colleagues, enabled the widespread use of medicinal products extracted from human plasma.

Improvements in protein purification and molecular separation technology have made available a wide variety of products, with medical applications covering a large field, and the therapeutic value of these is unquestioned. However, the potential for viral transmission is well recognized, and because of the large number of donations which are pooled, a single contaminated batch of a plasma-derived product, with the contamination possibly originating from a single donation, can transmit viral disease to a large number of recipients. The recognition in the mid-1980's that

plasma-derived medicinal products, in particular coagulation factor concentrates, had caused widespread transmission of human immunodeficiency virus (HIV) and hepatitis C (previously identified as non-A non-B hepatitis) resulted in major changes to the manufacturing processes, with the introduction of specific steps to inactivate or remove these and other blood-borne viruses. Infectious non-enveloped viruses were detected in certain plasma-derived medicinal products during the 1990's and early 2000's. Therefore, recent process development has been devoted to further reducing non-enveloped viruses such as hepatitis A (HAV) and parvovirus B19 (B19V).

Measures taken to prevent infection include selection of donors, screening of individual donations and plasma pools for markers of infection with known viruses and validation of the production process for inactivation or removal of viruses. From the 1990's on, measures designed to minimize contamination of the starting plasma have been improved by the refinement of serological test kits and the use of nucleic acid amplification technology (NAT) for the testing of viral DNA and RNA, thereby shortening the window period during which infectious donations are not detected.

2. SCOPE

Blood products are Medicinal products derived from human blood and human plasma which fall under the definition:

"Medicinal products based on blood constituents which are prepared industrially by public or private establishments, such medicinal products including, in particular, albumin, coagulating factors and immunoglobulins of human origin." Furthermore, the pharmaceutical legislation also applies to plasma that is prepared by a method involving an industrial process. Solvent-detergent treated plasma is an example of this latter category.

Many parts of this guideline could also be applicable to active substances extracted from human cellular components such as haemoglobin.

The scope does not cover blood or blood components for transfusion medicine. Furthermore, it does not cover medicinal products prepared on a small scale for individual patients in accordance with a medical prescription, although many parts contained in this document may be pertinent.

3. LEGAL BASIS

This guideline has to be read in conjunction with requirements laid down in the GCC data requirements for human drugs submission and the guideline on the scientific data requirements for plasma master file (PMF), which is an additional element to the normal requirements of the common technical dossier (CTD) when submitting a marketing authorization application (MAA) for blood products. In essence, fulfilling the aforementioned requirements and complying with the reference pharmacopeia (e.g. USP, Ph. Eur.) standards for plasma-derived medicinal products are mandatory to ensure the quality and safety of blood product.

Furthermore, it is a legal requirement that before an authorization to market a plasma-derived medicinal product the manufacturer must demonstrate batch-to batch consistency. In addition, the absence of specific viral contaminants must be demonstrated to the extent the state of technology permits.

4. STARTING MATERIAL

The collection and testing of starting material are major factors in the quality assurance of the manufacture of biological medicinal products. Measures taken to reduce risks for transmission of blood borne infections by plasma-derived medicinal products include the meticulous control of starting material.

Starting material for fractionation is plasma, which either can be obtained from whole blood donations or by plasmapheresis and this has to comply with the USP general chapter "<1180> human plasma" and/or Ph. Eur. monograph "human plasma for fractionation".

All information on the starting material should be in accordance with the Guideline on the scientific data requirements for a plasma master file .It may be provided as a PMF.

It is also possible to provide the same information in Module 3, section 3.2.S. of the documentation for the medicinal product. The PMF should be updated and re-submitted for approval on an annual basis. Reference to more than one PMF is possible and should be clearly indicated in the dossier.

The immunization of donors to obtain immunoglobulins with specific activities should be in compliance with the requirements of the relevant pharmacopeia monographs (e.g. USP, Ph. Eur.).

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This also includes testing of donors of erythrocytes used for immunization of donors for anti-D plasma. This information which is specific to a particular product (e.g. immunization scheme used for specific immunoglobulins) should be included in section 3.2 S of the dossier for the relevant product and not in the PMF.

4.1. Risk Factors

Many factors can affect the safety of blood donations in transfusion medicine. However, not all of these are relevant to medicinal products derived from human plasma and manufactured on an industrial scale. Those, which have implications, are blood borne infections and include viruses found in plasma, which establish a viraemia such as HBV, HCV, HIV 1 and 2, HAV and B19V, or any other emerging infectious viruses or other agents such as vCJD. In many cases, such viruses can establish a persistent or latent infection.

In rare cases, medicinal products derived from human plasma have been shown to transmit viruses to recipients even where the starting material has been controlled for viral contamination in accordance with state of the art procedures. This is due to the nature of the starting material, which is obtained from a panel of heterogeneous human donors which cannot be virologically characterized as thoroughly as other sources of biological materials, such as cell banks.

Other factors of equal importance relate to the quality of the product, for example the integrity and biological activity of clotting factors and of immunoglobulins, which can be affected by the processing of the starting materials after collection. Therefore, the risk of generation of thrombogenicity and immunogenicity should be considered.

4.2. Selection of donors and testing of starting material

Selection of donors and testing of donations and plasma pools, are important factors in the safety of plasma-derived medicinal products:

4.2.1. Selection and exclusion criteria

Further guidance is provided in the Guideline on scientific data requirements for a plasma master file (PMF).

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4.2.2. Testing

Each donation should be tested in compliance with the USP general chapter "<1180> human plasma" and/or the Ph. Eur. monograph "Human plasma for fractionation". Plasma pools should also be tested according to the USP general chapter "<1180> human plasma" and/or the monograph "Human plasma for fractionation". Additional testing and specifications of plasma pools are required for specific products, e.g. virus inactivated pooled plasma and anti-D immunoglobulins. These monographs require testing for HBsAg, HIV antibodies, HCV RNA of each fractionation pool and additional testing for B19V DNA for specific products (i.e. virus-inactivated pooled plasma and anti D immunoglobulins) and HAV RNA for virus-inactivated pooled plasma.

If normal immunoglobulin for intramuscular/intravenous administration and/or albumin are used in the manufacture of anti-D immunoglobulin, the plasma pools from which they are derived should comply with the requirement of the respective pharmacopeia monograph on anti-D immunoglobulin. For validation of all testing methods, reference is made to the guideline on scientific data requirements for a plasma master file (PMF).

B19V has been transmitted by plasma-derived medicinal products such as coagulation factors, fibrin sealants, and by solvent-detergent treated plasma. In immuno-competent patients without specific underlying diseases, the infection is usually asymptomatic or mild. However, transient aplastic crisis may be observed in patients with erythropoietic disorders or prolonged anaemia may occur in immuno- compromised patients. Severe anaemia and non-immune hydrops fetalis can occur in infected foetuses. Highly viraemic donations occur quite frequently and may lead to high contamination levels of plasma pools with more than 108 IU B19 DNA per ml. It is recognized that NAT screening for exclusion of such high titer donations can significantly reduce the contamination of plasma pools thereby reducing the risk for transmissions and resulting potential complications. Therefore, introduction of high titer screening is encouraged. The appropriate limit for contamination of plasma pools depends on the B19V reducing capacity of the product-specific manufacturing process. A risk assessment according to chapter 9 of this guideline is performed in order to substantiate claims that a product can be considered safe with regard to B19V infections. It is important that the manufacturer clarifies whether all plasma used as starting material for a specific product is subjected to B19 NAT testing in order to allow a correct risk assessment.

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4.3. Traceability

A system has to be in place, which enables each donation to be traced from the donor via the blood establishment through to finished products and vice versa.

Traceability has to be maintained. It is strongly recommended that every time a product is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product[1].

Facilities, to which blood and blood components are delivered, including manufacturers, should retain traceability records for at least 30 years after the time of the donation. To ensure that the duration of traceability is not shorter for batches of medicinal products compared to their raw/starting materials, a link from donation/donor to finished product should be maintained by the manufacturer of the plasma- derived product for at least 30 years after the time of the donation. This is to ensure that the MAH for this product or a manufacturer, using a batch of a plasma-derived product in his product, and in Saudi Food & Drug Authority (SFDA) would be informed if, in exceptional circumstances, post- collection information would lead to measures regarding the product.

4.4. Post-collection measures including look back procedures

A post collection information system should be in place including a description of the measures for reporting of serious adverse reactions and events. The management of post-collection information which may affect the quality and safety of blood and blood components, including any serious adverse reactions caused by a donation, that in turn implicate other components from the same donor, should comply with the procedures laid down in the SFDA GMP requirements.

The management of post-collection information between the blood/plasma establishment and, where there is a PMF, the PMF holder, and the manufacturing/fractionation facility should be described in standard operating procedures. These should be in place at the blood establishment(s), the PMF holder (if applicable) and at the manufacturer(s) of the plasma-derived medicinal products

and subject to written agreements between parties. If the reliability of a blood establishment/center or the quality and safety of plasma could be questionable the PMF holder should inform the SFDA.

The following information should be communicated by the blood establishment to affected manufacturers of plasma derived medicinal products without delay after receipt of the information, if subsequent to donation:

a) It is found that the donor did not meet the donor health criteria relevant to plasma safety and/or quality;

b) A subsequent donation from a donor previously found negative for viral markers is found positive for any of the viral markers.

c) It is discovered that testing for viral markers has not been carried out according to agreed procedures between manufacturer/PMF holder (if applicable) and blood establishment;

d) The donor develops an infectious disease caused by an agent potentially transmissible by plasma-derived medicinal products (HBV, HCV, HAV, other hepatitis viruses, HIV 1 and 2, and other agents in the light of current knowledge) (see section 4.1);

e) The recipient of blood or of a labile blood component develops post transfusion an infection which implicates or can be traced back to the donor.

f) A donation is involved in look-back procedures initiated by the blood establishment in case of b, d, or e.

A look back procedure consists of tracing previous donations and testing of any retained samples within a timeframe of at least 6 months prior to the last negative donation. Any departure from a 6 month look back period should be clearly stated and adequately justified. However, the time should be at least equal to the maximum test specific window period prior to the last donation with a negative test result. The following should be considered:

- Donations, which have not been processed, should be identified and withdrawn from processing pending further investigation. The operation of an appropriate inventory hold (e.g. 60 days) may be helpful in this respect.

- In case the donation has been processed, an immediate evaluation should be made of whether the new information compromises the safety of batches of product and requires

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their withdrawal. This evaluation should take account of criteria such as the disease, the type of seroconversion, the results of further testing of the donation, possibly including testing by nucleic acid amplification technology (NAT), the sensitivity of the tests performed (on the individual donations, the mini-pools and the plasma fractionation pools), the size of the pool, the information on the cumulative look-back units that might be present in that particular batch and the implicated plasma pool, the nature of the product, its manufacturing method and the virus inactivation removal capacity of the process.

- A system for the compilation of the affected units for every plasma pool should be in place and the information should be kept together with the batch record of the affected finished product and the respective plasma fractionation pool(s) records to ensure that this information is readily available to the Qualified Person(s) responsible for the release of intermediates or finished products.

Where there are indications that a donation contributing to a plasma pool was infected with HIV or hepatitis A, B or C or vCJD, the case should also be referred to the SFDA with a risk-based evaluation by the manufacturer regarding continued manufacture from the implicated pool or of the need for withdrawal of batches of product(s).

The mutual information system between blood/plasma establishments and manufacturing/fractionation centers should include information about any donor who develops CJD or vCJD.

5. MANUFACTURE

The manufacture of plasma-derived medicinal products should be defined and justified in terms of strategy, and described with all relevant details regarding procedures, in-process controls and final controls. If the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated.

5.1. Risk arising during processing

In the manufacture of medicinal products derived from human plasma, consideration should be given to the following factors:

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- Microbial contamination may occur and may lead to the accumulation of pyrogens;

- Viruses and other adventitious agents may be introduced by reagents during manufacture (e.g., enzymes from tissue extracts or monoclonal antibodies used for affinity chromatography);

- The methods of manufacture may introduce process related impurities such as proteins, solvents, detergents, and antibodies or other ligands from chromatography;

- Methods of manufacture may modify the product resulting in adverse consequences for recipients, for example by the formation of product related impurities, such as neo-antigens, or by compromising the biological activity of the active component, e.g. by activation of coagulation factors leading to enhanced thrombogenicity. This is particularly of concern for steps introduced to inactivate or remove viral contamination which may affect the quality or yield of products. A thorough characterization, using state of the art methods, should be undertaken to ensure that functional characteristics are maintained and that aggregated, degraded or other modified forms, are appropriately controlled.

5.2. Plasma pools

The manufacture of plasma-derived medicinal products starts from defined plasma pools. Samples of each plasma pool should be stored for at least one year after the expiry date of the finished product with the longest shelf-life. A description of all relevant procedures for the preparation and the sampling of the plasma pools should be provided in part 3.2.S of the dossier of the medicinal product or by means of a reference to the PMF(s) where relevant.

In the dossier of the medicinal product all specifications of the plasma pool(s) should be stated. A clear reference to the PMF(s) is acceptable with respect to the description and testing of the plasma pool for viral markers, which should be performed according to the relevant pharmacopeia monographs. Where appropriate, compliance of the plasma pool with any production requirements of the relevant pharmacopeia monographs should be confirmed.

5.3. Intermediates

An intermediate plasma fraction (intermediate) is partially fractionated starting material which

must undergo further manufacturing steps before it becomes a bulk product or final product. Intermediates, commonly used for further processing into a final product, are fractions recovered from the process for the production of clotting factors (e.g. cryopaste) or from the production process of immunoglobulins or albumin (e.g. fractions II, III, IV, V), and may be prepared and stored by the product manufacturer or obtained from another supplier, a contract manufacturer.

The collection and control of starting materials for the production of an intermediate plasma fraction are important factors in the assurance of its quality. Information up to and including the production of the plasma pool should be provided in the Plasma Master File or in part 3.2.S of the dossier following the guideline on the scientific data requirements for a plasma master file (PMF). This information and information on the manufacture of the intermediate from the plasma pool should be provided to the manufacturer of the finished product. A contract should be established between the supplier of the intermediate and the manufacturer of the finished product. This contract should address information from the manufacturing process, traceability and specifications of the plasma and the intermediate, and the storage and transport of the intermediate. The Marketing Authorization Holder/applicant has final responsibility for the quality and safety of the medicinal product and therefore, should hold all the relevant information described in this section and have a contract with the manufacturer of the intermediate/finished product when different to the MAH.

For plasma-derived medicinal products, a variant of an established process may be employed if it concerns an intermediate plasma fraction. The suitability of using an intermediate manufactured by a variant process must be demonstrated by the manufacturer of the finished product. For the assessment of a possible impact on quality, the variant process should be validated as such.

Differences of a variant process, e.g. additional purification/extraction step, process conditions, intermediates, materials and equipment, should be listed and justified for each manufacturing site. Process combinations should be identified and validated. It should be demonstrated that the use of the variant process does not affect the quality and safety, including virus safety of the finished product. Comparability should also be demonstrated[7].

Storage periods for intermediates should be set and justified by stability data. When releasing a finished product produced from a stored intermediate, the finished product manufacturer should

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ensure that at the time of release the product meets current requirements regarding the risk of transmission of infectious agents. Intermediates produced from plasma or whole blood screened with virus marker methodology which has been superseded may be used during a transitional period, provided that a risk assessment has been performed, possibly supplemented by appropriate testing of manufacturing pools.

5.4. Manufacturing process

The strategies used in the manufacture of plasma-derived medicinal products are critical for product quality, safety and efficacy. Manufacturing strategies vary according to product and manufacturer, and usually include several fractionation/purification procedures, some of which may also contribute to the inactivation and/or removal of potential adventitious agents. Additionally, specific procedures to inactivate/remove viral contaminants should be a requisite part of the manufacturing strategy for all plasma products. Plasma-derived medicinal products are defined largely by reference to their method of manufacture, as with biological medicinal products in general. Therefore, the use of alternative processes is usually not acceptable.

While selection of donors and testing of donations are essential safety measures, incidents of virus transmission show that they are insufficient alone to ensure safety of the product. The manufacturing process itself plays a central role and is of great significance for products derived from plasma. Studies of a process for the ability to inactivate or remove virus infectivity will be subject to particularly careful evaluation when products derived from blood or plasma are considered. This will include consideration of the reduction in virus titer achieved, the rates of inactivation and the shape of inactivation curves, how robust the step is to process variables, and whether virus inactivation or removal is selective for a particular kind of virus.

The suitability of the various materials and procedures used in manufacture as well as the selected operating conditions, parameters and tolerances should be validated by correctly designed and interpreted studies.

5.4.1. Fractionation/purification procedures

5.4.1.1. Precipitation methods

Physical methods

Cryoprecipitation is most often used as the initial step for the production of Factor VIII concentrates. Subsequent purification techniques for FVIII include precipitation, adsorption of other coagulation factors, and chromatographic separation as well as procedures for virus inactivation to obtain the finished products. Cryoprecipitate-depleted plasma is commonly used for the preparation of other coagulation factors by adsorption/elution or chromatographic procedures and the residual plasma can be further processed to yield immunoglobulins and albumins.

Physical/chemical methods

Among these methods, the ethanol fractionation procedures derived from the Cohn method are the most widely used for albumin and immunoglobulins. They commonly incorporate several steps, in each of which compliance with specific requirements is decisive for product quality; some of these steps may also contribute to effective reduction of potential viral contaminants. Therefore, clear specifications for ethanol and protein concentration, temperature, pH and ionic strength, and time of treatment, with data on acceptable tolerance as well as the means of controlling them should exist.

Appropriate data should also be provided for methods relying on other chemical agents such as ethylacridin-lactate, caprylic (octanoic) acid, methanol, ammonium sulphate, polyethylene glycol, cationic detergents, which are sometimes used in the preparation of certain plasma derivatives, as a rule in combination with other purification procedures. Some of these substances may have an impact on virus safety such as caprylic (octanoic) acid, for others information is still scarce.

5.4.1.2. Chromatographic methods

A number of different chromatographic procedures may be used in the purification and manufacture of plasma-derived medicinal products. It has to be taken into account that the selectivity of the procedures and the yields depend critically on the quality of the chromatographic

resins as well as on factors like the capacity of the column, nature and concentration of proteins in the product, ionic strength and the pH of buffers, flow rate, contact time and temperature. The chosen procedures should be based on data of process development studies. All appropriate specifications and accepted tolerances should be stated, and control data documented.

The conditions of storage of the columns, preservation and elution of preservatives, sanitization and methods of regeneration should also be described. Details should be given of clarification and sterile, dia- or ultra-filtration procedures used.

5.4.1.3. Additional Considerations

Anticoagulants such as antithrombin and heparin may be added as raw materials/reagents at various stages during the production of coagulation factors to minimize activation. The materials, their use and residual concentrations in the final product should be documented.

The residual concentrations should be measured in the final product unless acceptable and consistent results have been demonstrated. Several other compounds like charcoal, bentonite, colloidal silica are sometimes used for clearing various impurities like pigments, lipoproteins etc. Details on the characteristics of the compounds, on their decontamination and on the operating conditions should be provided.

5.4.2. Virus inactivation/removal procedures

Procedures to inactivate/remove infectious viruses are included in the manufacturing strategies for plasma-derived medicinal products. The manufacturing process conditions and in-process monitoring for virus inactivation/removal steps should be clearly defined and justified. Careful validation is needed for each inactivation/removal step ensuring that the validation includes worst case conditions. The integrity of the product should be demonstrated under established manufacturing conditions. For further information, reference is made to section 8 Adventitious Agents.

It is essential that material that has been subjected to a virus inactivation/removal step should be segregated from untreated material to prevent cross-contamination[2].

5.4.3. Process validation

Validation studies should be carried out by each manufacturer for the specific processes used and, unless otherwise justified, for each production site. Moreover, if studies involve modelling the process on a reduced scale, they should be capable of mimicking satisfactorily the conditions of full scale production and the suitability of the modelling should be demonstrated.

In the development of the manufacturing process, critical parameters and critical controls should be identified and controlled. This is particularly important for novel process designs, including new designs for products traditionally manufactured using ethanol fractionation. The effectiveness of a given manufacturing process in consistently yielding a product with expected quality and biological activity should be documented with data based on a broad set of relevant analytical methods. Particular attention should be paid to demonstration of removal of process- and product-related impurities, for example chemicals used for, or derived from fractionation/purification procedures, and naturally occurring substances which may be hazardous, such as blood group substances and activated coagulation factors. Spiking experiments with certain potential contaminants may be necessary to demonstrate the clearing efficiency of the process.

The studies should be designed to justify the selected operating conditions and the acceptable tolerances, including worst case conditions, and to document their adequacy in achieving the expected process performances.

When chromatographic columns are used, conditions leading to overloading as well as leaching from the gels, particularly in the case of affinity chromatography with potentially harmful ligands, should be carefully investigated. Attention should also be paid to the cleaning and regeneration of the columns with particular emphasis on pyrogen elimination and virus carry over. The criteria for the use and re- use of chromatography resins and their life time should be provided. This is also applicable to filters in case of re-use.

For the establishment of release specifications of blood products , reference is made to the general principles laid out in the ICH guideline (Q6B)3. The manufacturer should demonstrate consistency at full scale production, showing compliance with the established specifications of the product. To this aim, batches should be derived from different bulks. In case that the manufacturing process

starts from different amounts of plasma, it should be shown that the process yields a comparable product under the range of conditions applied. If a manufacturer decides to use intermediates from different manufacturing sites it should be shown that comparable products are consistently obtained. In the case of different manufacturing sites used in parallel a detailed validation program should be presented to demonstrate consistency.

Reprocessing should only be performed in case of process failures. The procedures and criteria should be fully described. Validation data should demonstrate that repetition has no negative influence on product quality.

6. QUALITY CONTROL

6.1. In-process controls

The procedures for production and equipment monitoring, the production steps where control tests are carried out, the means of sampling and of storing the samples, as well as the testing procedures should be described.

The pooling of starting materials should be subject to careful control to avoid contamination and introduction of foreign material.

The monitoring of relevant parameters during manufacture, such as pH, temperature, ethanol concentration, protein and potency where appropriate, as well as the results from bacterial counts and endotoxin should be documented. Identification of critical in-process controls and limits for these parameters should be justified in line with the ICH guideline (Q6B).

6.2. Quality control of products

All products must comply with the appropriate pharmacopoeia monographs (e.g. USP, Ph. Eur.).

All relevant parameters should be measured in each batch of the final product. In addition, measurements should be made of substances used during formulation or during production, e.g. residual solvent/detergent concentrations where these have been used. Appropriate limits for all these parameters should be set reflecting the capability of the production process in line with ICH Guideline (Q6B). For certain parameters, testing of either the drug substance or the drug product may not be necessary on a routine basis and may not need to be included in the specifications if

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efficient control or acceptable and consistent results have been satisfactorily demonstrated.

Batches which are used as in-house reference materials should be sufficiently characterized and their intended purpose specified. Any differences in their manufacturing process in comparison to the commercial process should be clear. A procedure for replacement of reference materials should be established.

The variability of the starting material and the heterogeneity of the plasma-derived medicinal products are important considerations in the validation of analytical methods used for starting materials, in- process controls, active substances and medicinal products. Validation for analytical procedures should be performed according to the ICH guideline (Q2(R1))4. Suitability of methods described in specific monographs also needs to be demonstrated taking into account product specific aspects, such as matrix interference. If reference is made to compendia methods (e.g. USP, Ph. Eur.) that are described in general terms (e.g. immunochemical methods 2.7.1), validation studies should also to be performed. If methods other than those specified by the pharmacopoeia (e.g. USP, Ph. Eur.) are used, the alternative procedures should be shown to give consistently equivalent results on several batches of product.

United States and European pharmacopoeia monographs for plasma derived-medicinal products are revised to encourage the use of alternative tests to the rabbit pyrogen test.

7. STABILITY STUDIES

Stability studies should be performed according to the GCC Guidelines for Stability Testing. The MAH should ensure that stability studies on the intermediate and, unless otherwise justified, on the finished product are performed if an intermediate from an external manufacturing site is introduced.

8. ADVENTITIOUS AGENTS

8.1. Manufacturing process design

General principles concerning the incorporation of virus inactivation/removal steps in the manufacture of biological products are outlined in the ICH Q5A(R1) and EMA guidelines [5,6]. This section contains further guidance relevant to plasma derivatives. The principles in both guidelines

should be taken into account when designing manufacturing processes or modifying processes to give further assurance of virus safety. The rationale for the choice of specific virus inactivation/removal steps deliberately introduced into the process should be given.

8.1.1. Incorporation of effective steps for virus inactivation/removal in the manufacturing process

For all plasma-derived medicinal products, it is an objective to incorporate effective steps for inactivation/removal of a wide range of viruses of diverse physico-chemical characteristics. Thus, it is desirable in most cases to incorporate two distinct effective steps which complement each other in their mode of action such that any virus surviving the first step would be effectively inactivated/removed by the second; at least one of the steps should be effective against non-enveloped viruses. It is recognized that it is difficult to inactivate or remove all known non-enveloped viruses efficiently using a single process step. Some non-enveloped viruses (such as animal parvoviruses) are stable against a number of heat-treatments while extremely small viruses (such as circoviruses) might penetrate even filters with small pore sizes designed for parvovirus reduction. Manufacturers are encouraged to develop/implement complementary process steps designed to remove or inactivate a wide spectrum of viruses. This will enhance confidence in safety including unknown potentially emerging viruses. It is recognized that designing steps that will complement each other and also be effective against a wide range of viruses, including enveloped and non-enveloped viruses of diverse physico-chemical characteristics, is not a straightforward task. Where a process step is shown to be reliably effective in inactivating/removing a wide range of viruses including enveloped and non-enveloped viruses of diverse physico-chemical characteristics and the process contains additional stages reliably contributing to the inactivation/removal of viruses, a second effective step might not be required.

Viruses tend to fall into two groups in this respect, those susceptible to a wide range of inactivation/removal procedures and those resistant. Also, there may be viruses potentially present in plasma that are resistant to the inactivation/removal methods that can currently be applied to a particular class of product.

Manufacturers should apply their best efforts to develop methods to inactivate/remove viruses and this should be a continuing process. Previous experience clearly shows that starting material may

contain unknown viruses and that new viruses may appear. This emphasizes the need to design processes to inactivate/remove as wide a range of viruses as possible. Even this may not preclude new or unknown infectious agents breaking through a process.

8.1.2. Contribution of partition processes to virus removal

Partition processes such as fractionation or purification procedures (e.g. chromatography) may contribute to virus removal. However, cases of virus transmission have occurred clinically with coagulation factors and intravenous immunoglobulins whose manufacture have relied purely on partition processes. Furthermore, partition processes involve a large number of variables that are difficult to control and are difficult to scale down for validation purposes. Minor differences in physico-chemical properties of viruses can have a major influence on partitioning which makes it difficult to extrapolate from validation studies. Partitioning may also be affected by the presence or absence of antibodies. Consequently, it may be difficult to demonstrate that partition processes are reliably effective.

If a partition process gives reproducible reduction of virus load, and if manufacturing parameters influencing the partition can be properly defined and controlled, and if the desired fraction can be reliably separated from the putative virus-containing fraction, then it could fit the criteria of an effective step. Previous experience can be taken into account to design experiments for validation of virus removal by fractionation.

Since fractionation can contribute to virus removal, particular attention needs to be given to validation studies and clinical safety if novel manufacturing processes depart from standard fractionation techniques.

8.1.3. Effect of virus inactivation/removal steps on the product

It should be established that the virus inactivation/removal steps selected will contribute to the overall safety of the product and any potential interaction between the steps should be considered. Consideration should also be given to the maintenance of the integrity of the components of the plasma derivative and clinical efficacy, to the potential for formation of neo-antigens, to the possibility of enhanced thrombogenicity from activated coagulation factors, and to the possibility of toxic residues from chemicals used in the process as well as to virological safety.

8.2. Virus inactivation/removal procedures

The following is not a comprehensive account of available virus inactivation/removal procedures and points to consider but identifies some common criteria that need to be considered for certain processes.

8.2.1. Precipitation with ethanol

Ethanol fractionation may contribute to the virus safety of albumin and immunoglobulins by removing adventitious viruses rather than inactivating them. In fact, the disinfectant effect of ethanol/low pH occurs mostly at room temperature or above, whereas plasma fractionation is carried out at a low temperature to avoid protein denaturation. Where differential partitioning of the plasma components and viruses occurs during the precipitation steps, this will result in the removal of viruses with the discarded fraction. Furthermore, precipitated proteins can be separated by centrifugation or, alternatively, by filtration. Filter aids are used to prevent clogging of the filters and they can enhance the virus removal capacity of the separation process.

8.2.2. Heating in aqueous solution

Heating in aqueous solution at 60°C for 10 hours in the final container is the pharmacopoeial method for virus inactivation for albumin preparations. This method of inactivation is also used for bulk preparations of several other plasma-derived medicinal products. It has been shown that pasteurization is an effective inactivation step for enveloped and some non-enveloped viruses. The efficacy of such a treatment is dependent upon the composition of the solution, the temperature and incubation time. Stabilization may be necessary to protect proteins and minimize neo-antigen formation but stabilizers can also protect virus from inactivation and therefore have to be chosen carefully.

8.2.3. Heating of lyophilised products

The effectiveness of virus inactivation may vary according to the characteristics of the lyophilisate and the heating conditions. Upper and lower limits of residual moisture should be set based on virus validation studies as well as protein integrity studies and aggregate formation studies. Where such a treatment is applied to the product in its final containers, the variation in residual moisture between vials of product should be within the limits set. Residual moisture is a particular critical

parameter and should be preferably measured on each vial with non-destructive methods (e.g. by near infrared spectroscopy). Temperature and duration of heating should be monitored throughout the process step.

8.2.4. Solvent/detergent treatment

Treatment with a solvent such as tri-n-butyl-phosphate (TNBP) combined with a non-ionic detergent such as Triton X-100 or Tween 80 can inactivate enveloped viruses. Prior to such treatment, in-process solutions should be free from gross aggregates that may harbour virus and protect it from the treatment. This can be achieved by filtration which should be done prior to addition of the solvent/detergent or if done after, the filters should be demonstrated not to alter the levels of these additives in the incubation solution. Physical validation must demonstrate that mixing achieves a homogeneous mixture and that the target process temperature is controlled throughout the bulk solution for the duration of the defined incubation time. In-process checks should be carried out to confirm that the correct amounts of solvent and detergent have been added. Residual levels of solvent and detergent should be minimized by processing and carefully monitored in the final product. Non-enveloped viruses will not be inactivated by this process.

Solvent/Detergent (S/D) treatment is an established procedure for virus inactivation. Previous experience can be taken into account to design experiments for validation of virus inactivation. This can be helpful to limit the number of product-specific validation runs to the determination of virus inactivation kinetics at "worst case" conditions (e.g. lower manufacturing limits for concentration of SD-reagents and temperature). Since a high lipid content could affect the efficacy of inactivation, this should be considered at validation in cases where the product intermediate contains significant amounts of lipids.

8.2.5. Virus reduction filtration

There may be difficulties with removing the smaller viruses by filtration while maintaining a satisfactory yield of product, especially for material of high molecular weight such as Factor VIII. Certain types of filters may cause activation of coagulation factors; this should be minimized by suitable choice of filter material and activation should be monitored before and after filtration.

The mode of action of the particular filter selected should be described and the parameters critical

for virus removal (e.g., volume per filter area, ionic strength, pH, flow rate, pressure and protein load) should be identified. These critical parameters should be used to define appropriate virus validation studies. Tests to confirm filter integrity are essential in-process controls. In addition, the performance of filters used in virus validation studies must be compared to that of the filters used in routine production.

Aggregation of viruses can affect the level of virus removal by filtration. This should be taken into account when performing validation studies with viruses which will have been propagated and concentrated under laboratory conditions and whose state of aggregation may differ from that expected of a virus present in plasma. Information on the characterization of the filter material by the manufacturer should also be provided.

Complex formation with antibodies as well as the protein content of the solution or adsorption of the viruses to membrane surface and the composition of the intermediate (e.g. buffer composition) can have an important impact on the removal of viruses. This should be considered in virus validation studies as well as in routine production processes.

8.2.6. Low pH

Low pH (approximately 4) can be effective for immunoglobulins to inactivate enveloped viruses and certain non-enveloped viruses (e.g. B19V has been shown in some studies to be inactivated, whereas HAV and animal parvoviruses are not). Additionally, enveloped viruses may be inactivated at low pH in ethanol-containing intermediates in albumin production.

For both enveloped and non-enveloped viruses, the reduction factors that have been demonstrated depend on the exact conditions (e.g. pH value, time and temperature of treatment, composition of the solution, etc.) and the virus strain used in validation studies.

8.3. Points to consider for specific products classes

8.3.1. Coagulation factors

As for all plasma-derived medicinal products, effective process steps for the inactivation/removal of enveloped viruses are essential. Non-enveloped viruses such as hepatitis A and B19V have been transmitted by this class of products. For Factor IX products, steps should be included in the

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process that are effective for HAV and B19V. Since steps like heat inactivation may have some limitations regarding certain non-enveloped viruses, companies are encouraged to increase the safety with regards to small, heat-resistant, non-enveloped viruses by use of removal procedures, like virus reduction filtration (also known as nanofiltration), where this is technically feasible.

For Factor VIII (and Factor VIII /von Willebrand Factor), von Willebrand Factor and fibrinogen products, where the large molecular size renders a size-based separation from virus particles less feasible, at least one step in the manufacturing process should be effective for HAV for which inactivation procedures have shown to be applicable. It is recognized that some viruses (e.g animal parvoviruses) are very resistant to physico-chemical methods for virus inactivation and that development of an effective inactivation/removal step may be difficult for this type of virus. B19V may be inactivated by carefully designed heat treatment steps (pasteurization in an appropriate matrix or dry heat treatment at appropriate residual moisture). Parvoviruses may be removed by virus filtration depending on the pore sizes applicable to the coagulation factors

8.3.2. Immunoglobulins

Immunoglobulin products have a good safety record for the known non-enveloped viruses due in part to the contribution from neutralizing antibodies in the product. However, the possible transmission of unknown or emerging non-enveloped virus or the decline of antibody titers to non-protective levels in donor pools cannot be totally excluded. Thus at least one effective virus inactivation/removal step for non-enveloped viruses is therefore required. Ethanol fractionation/precipitation steps can be accepted as effective for non-enveloped viruses if adequately controlled and validated. In the case that ethanol fractionation/precipitation steps are not found effective, another effective step for non-enveloped viruses should be introduced. If the process is based solely on chromatographic purification, an additional step(s) shown to be effective for non-enveloped viruses is needed.

Introduction of virus reduction filtration (small pore size 15-20 nm) into immunoglobulin processes has been shown to be effective for many non-enveloped viruses.

8.3.3. Albumin

Albumin manufactured by an established fractionation process that includes the terminal

pasteurization specified in the pharmacopoeia monograph (e.g. USP, Ph. Eur.), has an excellent virus safety record. However, further information is required from validation studies on the reduction of viruses during the manufacturing process. Validation of the pasteurization step should consider the nominal concentration of the finished product.

8.3.4. S/D Plasma

SD plasma has good safety measures for enveloped viruses and safety measures are in place for HAV and B19 (i.e. USP general chapter "<1180> human plasma" and/or Ph. Eur. monograph "Human Plasma (Pooled and Treated for Virus Inactivation"). The risk from other non-enveloped viruses already circulating in the population is considered low, because it is assumed that neutralizing antibodies are present in plasma pools. There remains a potential risk from newly emerging non-enveloped viruses. Therefore, manufacturers are encouraged to carefully follow the epidemiology of such viruses in their donor population.

8.4. Choice of viruses for use in validation studies

Viruses to be used in validation studies on plasma-derived medicinal products should include at least:

Enveloped viruses

<u>HIV-1</u>

It is not necessary to carry out additional studies with HIV-2 as it is similarly affected by inactivation procedures. HIV-1 is not required in robustness studies on established virus reduction steps, such as SD treatment, heat treatment and ethanol fractionation steps. For new reduction methods HIV-1 should be considered when there is a lack of evidence that robustness can be covered by other enveloped model viruses.

<u>Model for hepatitis C virus</u>

Biochemical characterization of HCV classifies it in the Flaviviridae related to both pestiviruses and flaviviruses. Currently, there are no methods available for propagation of the virus. Various models have been used to validate virus inactivation methods including pestiviruses, e.g. bovine

viral diarrhea virus, flaviviruses, e.g., WNV, TBEV or yellow fever virus, and togaviruses e.g. Sindbis virus. These viruses have properties in common with HCV. However, minor differences in physico-chemical characteristics of viruses can have major effects on how they partition. For example, there is evidence that pestiviruses differ in their partition in the Cohn Oncley fractionation process from togaviruses. Currently there are insufficient data on HCV to identify the most appropriate model virus for validation studies. Therefore, caution is required in the choice of a model virus and in the interpretation of validation data. The pestivirus BVDV may be more difficult to reduce in some partitioning steps and it may be more resistant at low pH than other model flaviviruses/togaviruses. Therefore, BVDV could be considered as a "worst case model" for HCV.

<u>Enveloped DNA viruses</u>

To date, there have been no recorded transmissions of a herpesvirus associated with the use of non-cellular blood components. However, since some herpesviruses may result in a viraemia, a validation study should be performed with an appropriate enveloped DNA virus, e.g. a herpesvirus such as pseudorabies.

Currently, there is no practical test system for hepatitis B virus validation. An animal virus model, the duck hepatitis B virus (DHBV), may be used as a model of human HBV. However, it requires the use of its natural animal host (duck or primary duck cells) for titration. In consequence, there is no general requirement to include DHBV in the virus panel. However, in some specific situations where the efficacy of new inactivation procedures (e.g. UV illumination) are highly virus dependent among enveloped viruses and for which inactivation/removal efficacy cannot be extrapolated from limited number of model viruses, the use of DHBV could be requested.

Non-enveloped viruses

The package of validation studies on non-enveloped viruses should establish the range of viruses susceptible to the inactivation/removal processes and identify the limits of the process. For example, a heat inactivation step used in the manufacture of a coagulation factor might be effective against hepatitis A virus but ineffective against another non-enveloped virus.

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Hepatitis A transmission has been associated with certain coagulation factors. HAV should be used for validation studies for coagulation factors as it is thought to be significantly different to other picornaviruses. Consideration should be given to the possible interfering effects of antibodies.

Validation studies for coagulation factors should also include an appropriate model for B19V. Models that have been used include canine, porcine, murine and bovine parvoviruses.

Studies using HAV and B19V are not required for immunoglobulins. However, data from non-antibody complexed model viruses may not adequately reflect reduction of HAV or B19V in intermediates where binding antibodies are present. Therefore it may be helpful (but not mandatory) to perform such studies in order to clarify the reduction capacity for HAV and/or B19V. In each case, studies with non-enveloped viruses for which antibodies are unlikely to be present should be performed to evaluate the ability of the process to inactivate/remove possible unknown non-enveloped viruses.

Model viruses for virus reduction filtration (nanofiltration)

Our knowledge of the virus clearance efficacy of nanofilters has improved with increasing use of nanofiltration in manufacturing processes. Clearance efficiency should be demonstrated for each product with a range of virus sizes whatever the nanofiltration system used. In some circumstances (e.g. immunoglobulin; pH; residual solvent/detergent), the quantification of virus removal solely by the filter may be rendered difficult by virus inactivation/neutralization that can occur during the nanofiltration. Robustness studies may focus on the most difficult viruses to remove with a particular filter. For small pore size filters designed for removal of small non-enveloped viruses, HIV and BVDV should still be part of the virus panel, but robustness studies may focus on small non enveloped viruses. For medium pore size filters, designed for removal of medium-sized viruses, HIV and an enveloped virus such as BVDV should be included in validation studies, with robustness studies focusing on for example BVDV.

8.5. Difficulties in the design and execution of virus validation studies

Reliable experimental demonstration of the effectiveness of virus inactivation and removal during the processing of plasma and the interpretation of data may be rendered difficult for various reasons. The presence of antibodies may affect partition of viruses or their susceptibility to

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chemical inactivation and may also complicate the design of the study by neutralizing infectivity. Furthermore, undiluted plasma or derived fractions are usually toxic for cell cultures used for virus detection as is the presence in intermediary products of chemicals such as ethanol and ethylacridinlactate. Therefore, assays may have to be preceded by procedures designed to counteract these effects, such as dilution, dialysis, etc. In addition, the product itself or chemicals used to prepare or to treat it may change the properties of viruses, for example leading to their coating and/or aggregation, which may result in difficulties in reliable quantification of residual infectivity.

In some situations, NAT can be an alternative to infectivity tests to measure virus load and determine reduction capacities of removal steps. When performing validation studies with NAT, careful characterization of the virus spike should be carried out in order to ensure the reduction of intact particles is measured and not removal of free nucleic acid or damaged particles. NAT studies may be useful to distinguish removal from inactivation when they occur at the same process step (e.g. caprylate fractionation steps) or when an infectivity assay is not feasible (e.g. due to neutralizing antibody interference).

8.6. Strategy for introduction of additional process steps for inactivation and removal of viruses

Since manufacturers should apply their best efforts to develop methods to inactivate/ remove viruses and this should be a continuing process, manufacturers should keep this under constant review in the light of technological developments. This is particularly important for products where there are currently limitations in what can be achieved in the reduction of non-enveloped viruses. Where it has been identified that specific process/product improvements can be made, applicants for MAA should set and justify timetables for such developments; and commit themselves to providing regular reports to the SFDA on their progress. Timescales for introduction of process changes should reflect the manufacturer's best efforts. In the meantime, product literature should be critically evaluated to provide relevant and specific information to enable clinicians to make an informed choice of product[1].

8.7. Revalidation

New validation studies are required when relevant changes in the manufacturing process or in individual steps are being undertaken. The absence of new validation studies should be fully justified. Any virus transmission seen in clinical use should result in an evaluation of available data by manufacturers and regulatory authorities so that appropriate action can be taken.

8.8. Investigation of reduction of TSE agents

All issues concerning reduction of TSE agents should take place according to the GCC data requirements for human drugs submission.

9. ASSESSING THE RISK FOR VIRUS TRANSMISSION

9.1. 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[1]. 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.

9.2. General principle of the risk assessment

The principle of the risk assessment is to consider various factors, such as epidemiology, viraemic titer, 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 virus 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

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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.

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 titer 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 titer. With respect to individual screening by specific tests (serological or nucleic acid amplification technologies (NAT)), the titer of viraemic donations that are not recognized 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.

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Virus inactivation/removal capacity

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 virus 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.

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 neutralization 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 virus neutralization 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.

Estimation of virus particles in the finished product

As a general principle for a safe product, the virus inactivation/removal capacity should clearly

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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 virus reduction factor is subject to various qualitative aspects of interpretation and the potential number of virus 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 virus input to estimate the number of virus particles per vial. The estimated number of virus 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 virus reduction factor obtained from validation studies.

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 virus genomes as an indicator of potentially infectious virus particles in the starting material should be followed. In-vitro infectivity data is generally not acceptable.

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 virus 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

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emerging viruses or viruses that have not been carefully considered by a surveillance system (such as B19V).

9.3. Application of this chapter

A virus risk assessment for HIV, HBV, HCV, B19 and HAV should be performed for all new marketing authorization applications (MAA) with the exception of albumin (see below). This will substantiate statements on virus safety and any remaining potential risk in the SPC1.

For products for which a marketing authorization 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 authorizations in the case of albumins manufactured according to pharmacopoeia specifications and with established Cohn or Kistler/Nitschmann 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.

The SFDA 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 contaminated donation has entered the manufacturing plasma pool. In such situations, reference can be made to the risk assessment included in the Common Technical Document dossier (CTD). A specified NAT limit of the manufacturing pool may be helpful in substantiating such risk assessments.

10. PLASMA-DERIVED PRODUCTS USED IN THE MANUFACTURE AND FORMULATION OF MEDICINAL PRODUCTS OR AS ANCILLARY BLOOD DERIVATIVE

Plasma-derived products are widely used in the manufacture of other medicinal products, as raw materials (e.g. albumin used in cell culture media), as reagents (e.g. antithrombin added during Factor IX concentrate production), as active substances (e.g. radiopharmaceuticals) or as excipients (e.g. albumin added to plasma-derived products, vaccines and recombinant DNA

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products or antithrombin added to prothrombin complex concentrates). In addition, plasma-derived products are used as ancillary blood derivatives and are evaluated by analogy to the medicinal product legislation.

10.1. Link to post collection information

The dossier requirements referred to in this guideline for starting materials and for traceability, from blood/plasma donations through to finished product and vice versa, also apply to plasma-derived products used in the manufacture and formulation of other medicinal products or used as ancillary blood derivative. This includes a contract between the manufacturer of the plasma-derived product and the manufacturer of the finished medicinal product in which maintenance of traceability records for at least 30 years after the time of donation is specified.

10.2. Quality and specifications

Whenever a plasma-derived product is used in the manufacture of a medicinal, it should have the same quality and specifications as that of the product for therapeutic use. For medicinal products, full documentation on quality should be provided for the plasma-derived product used. However, if a plasma-derived product is used as excipient and if 1) this product has a marketing authorization in the SFDA and 2) the starting material plasma used for the manufacture is linked to a submitted a plasma master file, then a complete documentation on quality may not be necessary. In this case a compilation of the manufacturing flow chart, the finished product specifications, summary of stability data including the approved shelf-life, virus risk assessment, and the qualitative and quantitative composition could be accepted. The plasma-derived product used in the manufacture should always be within its shelf-life and, therefore, within its marketing authorization specification at the time when it is incorporated into a starting material, intermediate, final product. In these circumstances, the development and testing of the product in which it is incorporated (e.g. pharmaceutical development, in-process and final product testing, and stability studies) will indicate the suitability of the plasma-derived product used in the manufacture. With regard to stability, no specific studies for finished products including excipients/reagents of different ages are required.

10.3. Synchronization of expiry dates

When a plasma-derived product is used as an excipient or ancillary blood derivative, synchronization of expiry dates with the finished products recommended 1) to help ensure that the plasma-derived product used as excipient of other products or as ancillary blood derivative complies with current recommendations for donor selection, donation screening and plasma pool testing and that state-of-the-art testing methods are used for these purposes and 2) to help ensure that the pharmaceutical characteristics comply with the current requirements.

It is recognized that, in some circumstances, it can be difficult for a manufacturer to synchronize the expiry date of a batch of the plasma-derived product used as excipient or ancillary blood derivative with the expiry date of the formulated product. Any deviation from this recommendation should be justified, as part of the Marketing Authorization procedure or consultation procedure.

Each time the requirements for a plasma-derived product or its starting materials are changed, the effect of the change, including impact on safety, will be evaluated, not only for its use as an active substance, but also for its use in the manufacture of medicinal products or as ancillary blood derivative. This evaluation will determine the action to be taken.

10.4. Albumin

Albumin manufactured according to established processes has an excellent clinical safety record during the last 50 years with regard to transmission of blood-borne viruses. However, the risk of infectious diseases due to the transmission of infective agents cannot be totally excluded when albumin (and other plasma-derived products) are used in the manufacture and formulation of medicinal products or as ancillary blood derivative.

As a single batch of albumin may be used to produce a number of batches of a medicinal product because of the small amounts that are typically used as an excipient or ancillary blood derivative, a careful selection of the products is recommended to limit the possibility of large volume product recalls where a donor to a plasma pool subsequently develops vCJD.

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