



**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE  
(CHMP)**

**DRAFT**

**GUIDELINE ON XENOGENEIC CELL-BASED  
MEDICINAL PRODUCTS**

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Comments should be provided using this [template](#) to [veronika.jekerle@emea.europa.eu](mailto:veronika.jekerle@emea.europa.eu)  
Fax + 442074188545

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# GUIDELINE ON XENOGENEIC CELL-BASED MEDICINAL PRODUCTS

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## **1. INTRODUCTION (background)**

Xenogeneic cell-based therapy is the use of viable animal somatic cell preparations, suitably adapted for: (a) implantation/ infusion into a human recipient or (b) extracorporeal treatment through bringing (non-human) animal cells into contact with human body fluids, tissues or organs. The principal objective is reconstitution of cell/tissue/organ functions. The genotype and/or phenotype of the cells may have been modified, e.g. by isolation, culture, expansion, pharmacological treatment or combination with various matrices.

This guideline is an annex to the guideline on cell-based medicinal products (EMA/CHMP/410869/2006) and deals specifically with requirements unique to xenogeneic specificities. This document is intended to provide general principles to be taken into consideration for the development and assessment of xenogeneic cell-based products without prejudice to medical practice or national legislation, which may be applicable.

The main scientific and technical issues so far identified concerning the sourcing and testing of animals, manufacture, quality control, as well as the non-clinical and clinical development of xenogeneic cell-based medicinal products are addressed. Relevant public health aspects are discussed and measures to ensure a proper surveillance for infections, including zoonoses are highlighted. Attention is also given to principles of animal health and welfare in the processes of sourcing of xenogeneic materials for the medicinal products intended for human use.

These general principles may apply to a range of products using animal tissues as the starting material, as the key objective is to ensure that the product to be administered is of acceptable quality and standard, and free from contamination.

## **2. SCOPE**

This Guideline addresses the scientific requirements for xenogeneic cell-based medicinal products for human use.

Xenogeneic cell-based medicinal products contain viable animal cells or tissues as the active substance. Xenogeneic materials might be sourced either from non-transgenic or transgenic animals. The animal cells can also be genetically modified.

Although not within the scope of the guidance, some of general principles of this guideline will apply to viable animal cells used as raw materials (e.g. feeder cells) for cell-based medicinal products manufactured from human cells.

## **3. LEGAL BASIS**

This guideline should be read in conjunction with:

- The introduction and general principles (4) and part 4 of the Annex I to Directive 2001/83/EC<sup>1</sup> as amended;
- Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products<sup>2</sup>.
- Directive 2001/18/EC when cells are obtained from genetically modified animals.

## **4. MAIN GUIDELINE TEXT**

### **4.1. RISK ANALYSIS**

The general risk criteria and principles for the risk assessment defined in the Cell-based Guideline (EMA/CHMP/410869/2006) also apply for xenogeneic cell-based medicinal products. In addition specific concerns should be considered: The human use of xenogeneic cells/tissues is associated with several obstacles, including, but not limited to, management of the risks of transmitting known and

unknown pathogens. Importantly, there is a potential risk of introducing new infectious diseases into the general population through adaptation in an immuno-suppressed host. The risk of immunological rejection of animal cells/tissues is yet to be prevented and overcome, and there is the challenge of maintaining the survival and functions of the xenogeneic cells in the long term. The use of immunosuppressive treatment carries substantial risks due to a weakening of host defence mechanisms. The presence or absence of barriers isolating the cells from the immune system of the recipient should be part of the risk assessment. These risks may be minimized by careful choice of donor animals, reproducible manufacturing process, accurate non-clinical and clinical testing and monitoring as well as a risk management programme including infectious agents.

Moreover, there are uncertainties with the ability of the administered cells/tissues to provide the desired function over the intended time of use. The documentation should address risks at all stages of the procedure starting from the selection of donor animals to the administration of the product.

For an individual patient, the benefit/risk of treatment with xenogeneic medicinal products is influenced by the available therapeutic alternatives and the seriousness of the conditions to be treated. Because of the range of possible *in vivo* and extracorporeal uses and choice of animal species, the risk assessment should be made on basis of the specific characteristics of the product. However, the risks of the treatment must also be evaluated from the public health and environmental point of view.

## **4.2. QUALITY AND MANUFACTURING ASPECTS**

Three steps have been identified in the production of the xenogeneic cell-based product, which require specific consideration:

- source of animals
- procurement (extraction of organs/tissues or cells)
- processing

Procurement and processing of the xenogeneic materials needs to be performed in facilities separated from the animal facilities.

The manufacture of the active substance starts at the receipt of the animal starting materials in the GMP approved manufacturing facility.

### **4.2.1. Starting and Raw Materials**

Various organs, tissues and cells may be the starting material for xenogeneic cell-based products. The health status of the animals should be monitored and documented. Special attention should be given to organ/tissue specific pathogens that might pose a risk.

#### **1. Selection of the animals**

Source animal species may be those typically reared for consumption or conventional laboratory animals. The origin and derivation of source animals should be fully described considering possible infectious agents and diseases of the particular animal species. Founder<sup>1</sup> and source animals should be healthy and should, at minimum, be Specific Pathogen Free (SPF) and raised in SPF conditions, including health monitoring and barrier systems<sup>2</sup>. External stresses on the barriers should ideally be minimised.

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<sup>1</sup> Founder animals are the animals from which source animals are initially bred.

<sup>2</sup> In principle, the level of microbial control in animals can be set on three different levels:

- Germ-free gnotobiotic animals. The establishment of gnotobiotic animals requires delivery by hysterectomy and maintenance in isolators under positive pressure for their entire life span. These

Information should be available on the feeding history (e.g. the nature of manufactured feedstuff) of each source and founder animal.

When source animals die, or are euthanised, a full necropsy should be performed to identify clearly the cause of death and, where appropriate, archival samples should be obtained for storage. Herd records should be kept pertaining to the source animals and facilities.

When the source animal is sacrificed to harvest the organs/tissues, a full necropsy should be conducted including histopathological and microbiological evaluation. Samples should be archived for future examination.

Cells, tissues and organs intended for the manufacture of xenogeneic cell-based medicinal products should be produced only from animals that have been bred in captivity (barrier facility) specifically for this purpose and under no circumstances should cells, tissues and organs from wild animals or from abattoirs be used. Tissues of founder animals similarly should not be used.

### **Genetically modified animals**

Cells/tissues to be used in xenogeneic cell-based products may be obtained from genetically modified (transgenic or knock-out) animals, or may be obtained by *ex vivo* genetic modification. The modification might have been introduced either to express new properties in the cell, e.g. expression of human complement-regulatory proteins, or to modify specific antigenic structures, e.g. carbohydrate antigens like  $\alpha$  1-3 galactose terminal sugar residues, in order to reduce or minimise the risk of xenogeneic cell rejection. Genetically modified animals must be fully characterised and confirmation of the nature of the inserted or deleted gene must be given. In either case, genetically modified animals from which cells are obtained, have to comply with applicable European legislation. Animal cells from genetically modified animals used as active substance should comply with “Note for Guidance on the Quality, Preclinical and Clinical aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99). The Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (EMEA/CHMP/GTWP/125491/2006) contains guidance that can be applied to xenogeneic cell therapy as well.

## **2. Animal husbandry**

Procedures should be developed to identify and prevent incidents that negatively affect the health of the herd or colony, or that could negatively impact on the barrier facility or the SPF status of the herd.

SOPs should be present for:

- Detailing the housing of animals and containment conditions
- Water
- Bedding
- Performance and monitoring of health screening
- Removal from production and disposal of the animals and their by-products
- Identifying individual animals and recording their movements to, through and out of the facility
- Entry and exit of the animals
- Animal transportation
- Disposition of animal tissues and dead animals

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animals are devoid of all infectious agents except for those that are transmitted in the germline, e.g. endogenous retrovirus (ERV) or via intrauterine or transplacental pathways, e.g. herpes virus.

- Specific pathogen free (SPF) animals. The establishment of SPF animals can be achieved by hysterectomy of the dams and maintaining SPF breeding units of the descendent animals under barrier conditions to produce source animals.
- Animals free of designated pathogens/Qualified pathogen free animals. Source animals are from closed herds or colonies with documented health screening programmes. All infectious agents known to infect the species have to be considered.

- Source and handling of feed, including feeding
- Isolation and quarantine

### **Veterinary control**

Protocols for monitoring the herd for disease and infectious agents should exist. Specific screening procedures should include appropriate physical examination and laboratory tests. All infectious agents known to potentially infect the source species have to be considered including viruses, bacteria, mycoplasma, fungi, TSEs and parasites. The herd health surveillance system should include comprehensive documentation of all veterinary care received. The use of antibiotics and vaccination of source animals is not recommended. If the treatment of animals with any medicines is necessary for animal welfare reasons, an evaluation of the situation should be performed, and discussed with the competent authority. Any use of vaccines must be justified.

### **Quarantine**

All animals entering the facility have to be put under quarantine for a defined period to allow completion of screening procedures. Individual quarantine periods depend on the animal species and characterisation and surveillance of the animal herd.

### **3. Animal facilities**

A separate facility should exist for founder and source animals. Animal facilities should be isolated from each other to prevent cross-contamination and should be operated in such a way, including the use of biosecure barriers, as to minimise the exposure of the animals to infectious agents and to prevent cross-contamination both among animals and animals and humans.

In the preparation of feed, precautions should be taken to avoid chemical, physical and microbiological contamination. All feeding, bedding, water and utensils should be sterilized and animals disinfected (e.g. the outer surface of boxes). All feeding and bedding supplier should be approved and certified.

Environmental conditions, such as air flow (HEPA-filters, positive pressure) and water, should be routinely controlled and analysed. Programmes for cleaning, disinfection and sterilisation of the animal cages and pens after usage, and for disposal of waste including animals, feed, bedding, equipments, reagents, etc., should be established. The necessary microbiological quality control tests should be carried out.

An adequate number of staff should be available and should include veterinarians, either permanent or available on consultation. Animal caretakers should participate in a documented training programme and health monitoring of them, including vaccination history, should be recorded. SOPs on tasks and responsibilities of animal caretakers should be established.

Air treatment and handling and gowning procedures for personnel should prevent the transfer of animal diseases into humans and vice versa.

### **4. Transportation**

Transportation of source animals exposes them to risks not encountered in closed herds and should be avoided. In exceptional cases where transportation is necessary, barriers equivalent to, or better than, those in place at the facility, should be maintained during transit to avoid source animal contamination. Transportation should use dedicated vehicles in which the animals are not exposed to any other animals and the method has to be documented. Quarantine facilities should exist at the destination to allow for clinical evaluation upon arrival prior to acceptance for further processing.

For transportation of organs, tissues or even primary cells, procedures should be in place for appropriate shipping conditions in order to maintain the integrity of the materials and to avoid shipping errors and contamination.

## 5. Testing for infectious agents in source or founder animals

Source animals may carry known or unknown infectious agents. The acceptability of the source animal as a donor for tissues/organs or cells depends equally on prevention of infections and on thorough testing of the source animals.

Programmes for screening and detection of known infectious agents should be tailored to the source animal species and the manner in which the xenogeneic cell-based product will be used clinically. Programme testing protocols should be updated periodically to reflect advances in the knowledge of infectious diseases. Whenever applicable, guidelines related to human and veterinary medicines should be consulted (e.g. the CPMP Note for Guidance on the Production and Quality Control of Animal Immunoglobulins and Immunosera for Human Use - CPMP/BWP/3354/99).

The selected assays should be capable of detecting a broad range of infectious agents, as well as species-specific agents in the source animal. Appropriate *in vivo* and *in vitro* assays should be in place to characterise the potential of identified human pathogens. The putative pathogenicity of xenotropic endogenous retroviruses (ERV) and persistent viral infections in source animal cells, tissues and organs is of particular importance.

Assays used for the screening and detection of infectious agents should have well defined and documented specificity, sensitivity, reproducibility and validity in the setting in which they are to be used. Appropriate laboratory quality assurance standards must be exercised.

It is critical that adequate and validated diagnostic assays and methodologies for surveillance of known infectious agents from the source animal are available prior to initiating clinical trials.

Consideration needs to be given to screening the animals for the following infectious agents:

- their own recognised infectious agents and parasites
- endogenous retroviruses (ERV e.g. porcine ERV)
- known zoonotic agents transmissible to humans (e.g. rabies) and other zoonotic agents such as *Toxoplasma gondii* which are usually not considered zoonotic but which may infect through the therapy
- known infectious agents of humans
- infectious agents of humans relating to receptors expressed by transgenic animals, e.g. human complement-regulatory protein CD46 (membrane cofactor protein, MCP-1) as the cell-surface receptor for measles virus
- infectious agents known to have a high mutation or recombination potential such as influenza virus
- antibiotic-resistant bacteria
- geographically important infectious agents such as *Trypanosoma cruzi*, African Swine Fever

Consideration also should be given to:

- the commensal populations
- the possibility of transmission of latent infectious agents via the intrauterine pathway (herpesviruses)
- the usage of sentinel animals to screen for subclinical infections.

Founder and source animals should be free of known TSE-diseases and the feeding history since establishment of the source animal herd should be documented and should not raise concerns regarding possible transmission of a TSE agent. In the use of cattle, goat and sheep, the requirements of the CPMP/CVMP Note for Guidance on minimising the risk of transmitting animal spongiform agents via human and veterinary medicinal products (EMA/410/01- rev. 2 or any future revision) should be applied.

## **6. Procurement step**

The techniques used to collect animal materials should avoid contamination by the environment or by the operator.

Procurement of the animal cells/tissues/organs should ensure retrieval of the cells without affecting their intended final characteristics..

## **7. Archiving**

Long term archiving of tissue samples, cell preparations and paper records will be necessary. The archiving strategy should be adequate for the intended use of these types of products. Records should be kept for 30 years. Manufacturers should present to the authorities their plan for such long term archiving at the animal facilities as well as in the manufacturing plant. This is essential for proper monitoring of medicinal product quality and safety evaluation of exposed individuals in look-back procedures.

A protocol for archiving tissue samples should be established and validated to ensure traceability and the possibility for look-back. All samples to be archived must be collected carefully and should be as representative as possible. Archiving should be arranged in appropriate storage conditions and be protected from fire or flooding. There should be restricted access and nominated person/persons who is/are responsible for the archives.

Sampling should be planned so that various samples for different methods (e.g. pathology, hybridisation, antibody-testing, PCR) are available. Samples should include (at least) the tissue concerned (e.g. spleen, liver, bone marrow, CNS, lung), body fluids, and leukocytes. If sentinel animals are used, samples from them must also be archived in a similar manner as from the actual source animal. Samples must be stored either at -70°C (e.g. plasma) or in a cool dry dark place (e.g. for paraffin-embedded samples) depending on the method of collection, storage and further processing. Paraffin blocks are recommended for long-term storage.

All batches of xenogeneic cell-based medicinal products should be labelled so that the corresponding samples in the archives can be traced. Archived samples should not be used for any other purposes, such as research.

All records (e.g. herd feeding and health records, source animal health documentation) should be archived for a period at least equal to that of the archived tissue samples. This paper archive can be kept separately from the tissue sample archive. For electronic archiving, the computer systems need to be validated and appropriate precautions should be taken to allow retrieval of the electronic data up to the end of the archiving period (see chapter 4.5).

### **4.2.2. Manufacturing Process**

The requirements set for the manufacturing process of human cell-based products (EMEA/CHMP/410869/2006) are also applicable for medicinal products containing xenogeneic cells or tissues. Special care should be taken to prevent cross-contamination and transmission of adventitious agents, if cells/tissues of different origin are processed in the same premises.

### **4.2.3. Characterisation and quality control**

The requirement for characterisation and quality control of xenogeneic cells is identical to human cells (EMEA/CHMP/410869/2006).

Guidance for characterisation of genetically modified cells can be obtained from the Guideline on the Quality, Preclinical and Clinical aspects of Medicinal Products containing Genetically modified Cells (EMEA/CHMP/GTWP/28311/2007). The transgenes and vectors should comply with the Note for Guidance on the Quality, Preclinical and Clinical aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99).

When genetically modified animals are used for production of xenogeneic medicinal products, the characterisation should also address the presence of the transferred nucleic acid sequences in the cells and their expression.

### **Adventitious agents safety**

A risk assessment according the European Pharmacopoeia general text on viral safety should be performed to evaluate the possibility to harbour human viruses as well as transmitting zoonotic agents.

Although xenogeneic cell-based products are excluded from the scope of the ICH guideline on viral safety (Quality of Biotechnological Products: Viral Safety Evaluation of Biotechnology Products Derived from Cell lines of Human or Animal Origin CPMP/ICH/295/95), applicants may consult this guideline. The current World Health Organization (WHO) documents for use of animal cells may also be consulted.

Sensitivity and suitability of the methods used for the detection of zoonotic agents should be demonstrated. The possibility that replication competent and pathogenic endogenous retroviral elements in the xenogeneic cells could be mobilised and rearranged should be addressed. Additionally, the possibility that latent or persistent viruses (e.g. porcine gammaherpesviruses) could be reactivated and transferred from the xenogeneic cells should be assessed.

#### **4.2.4. Process Validation**

For xenogeneic cell-based products, the process validation requirements set in the guideline for human cell-based products are applicable (EMA/CHMP/410869/2006).

#### **4.2.5. Development Pharmaceutics (Formulation)**

The composition and formulation of the finished product should support the intended function of the cells or tissues. Suitability and biocompatibility of all materials of the finished product (including primary packaging material) and those to be used in administration should be demonstrated.

#### **4.2.6. Traceability and vigilance systems**

Traceability and vigilance systems equivalent to the systems established for human cell-based products should be in place for xenogeneic cell-based products from the supplier of the animals to the recipients and vice versa. For xenogeneic cell-based medicinal product traceability may also require to include data regarding not only the recipient but also from close contacts<sup>3</sup> including the health personnel (see 4.4.6.).

### **4.3. NON-CLINICAL TESTING**

Non-clinical testing programmes should be performed, wherever possible, in relevant animal models, in which the xenogeneic cells, including their bioactive molecules are active and can be compared to the human situation.

Expression levels, routes of administration and dosages should reflect the human situation to the highest possible degree.

Standard toxicological testing in animals, where the material is or is not active might add information on general effects of xenogeneic cells, such as production of unintended proteins/hormones, unintended homing of cells into tissues/organs, effects induced by rejection or encapsulation of xenogeneic cells and effects like graft versus host disease in immuno-suppressed animals.

The recommendations of the *Guideline on cell-based medicinal products* (EMA/CHMP/410869/2006) should be considered.

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<sup>3</sup> Close contacts are those that intimately share life on a daily basis, e.g. close family.

### 4.3.1. Pharmacology

The pharmacology of xenogeneic cells or the expression of a xenogeneic cell product should be first evaluated *in vitro* and subsequently *in vivo* as part of proof of concept. Safety endpoints could be addressed as part of proof of concept studies.

Non-clinical *in vivo* studies should provide the proof of concept for subsequent clinical trials. Non-clinical studies may provide valuable data to support the posology and concomitant (immunosuppressive) treatment chosen for human clinical trials.

Secondary pharmacodynamics and safety pharmacology should be considered on a case-by case basis.

#### Pharmacokinetics

The survival and adequate function of the administered xenogeneic cells including synthesis of relevant bioactive molecules should be studied.

Cells from xenogeneic cell-based products may migrate within the host, thus presenting clinical concerns regarding adverse reactions deriving from displaced, possibly differentiating bioactive cells or unexpected anatomical impediments. This should be evaluated in animals using histopathology complemented by an appropriate method for specific identification of the xenogeneic cells.

### 4.3.2. Toxicology

The need for toxicological studies depends on the product. However, as conventional study designs may not be appropriate, the scientific justification for the models used, or the omission of studies, shall be provided. The duration of observations in such studies might be much longer than in standard single dose studies, since the cells are supposed to function for a long time, which should be reflected in the design of these studies. The route and dosing regimen should reflect the intended clinical use.

The need for additional toxicity testing related to specific origin of the cells and specific xenogeneic molecules (e.g. carcinogenicity/tumourigenicity, reproductive / developmental and separate local tolerance studies) should be considered on a case-by-case basis.

### 4.3.3. Other toxicity studies

#### 4.3.3.1 Immunological and Immunotoxicity studies

In principle, xenogeneic cells induce vigorous immune responses by the host provided that the immuno-competent cells of the host come into contact with the xenogeneic cells or their parts. Studies should address, as relevant, the immunologic response of the host with or without immunosuppression to the xenogeneic cells, including their bioactive products.

Several approaches can be attempted for controlling immune responses, e.g. mechanical segregation of the cells, introduction into the animal cells of human genes coding for proteins that ameliorate the hyperacute rejection or control of the immune response, e.g. by immunosuppressive drugs, xenogeneic antigen deletion/modification (genetically modified animals) and tolerance induction. These methods raise different concerns that should be addressed in appropriate non-clinical studies.

The compatibility of the animal cells may be improved by physical separation from the host (e.g; encapsulation). In this situation, immunological studies may be useful to support the integrity of the barriers. The material used to encapsulate the cells may induce tissue reactions and should be addressed.

The selection or adaptation of the animal model should reflect the effects of the product and the therapeutic procedure as a whole. Among the effects to be monitored are:

- Induction of humoral and cellular responses and subsequent immunogenic reactions such as formation of immune complexes and complement activation.
- Necrosis or impaired function of the product due to the infiltration of immune cells into the xenogeneic graft or due to encapsulation

Immune modulatory properties of xenogeneic cell therapy, including the concomitant immunosuppressive regimen, can be addressed by studying the following parameters:

- Evidence of myelosuppression, such as pancytopenia, anaemia, leukopenia, lymphopenia, thrombocytopenia, or other blood dyscrasias
- Alterations in histology, including thymic atrophy or hypocellularity of immune system tissues such as the spleen, lymph nodes, or bone marrow
- Increased incidence of infections
- Increased incidence of tumours

Effects of immunosuppressive substances in order to maintain the xenogeneic cells and the direct immunoactivation or immunosuppressive effects originated by the xenotransplant should be differentiated, if possible.

The possible underlying mechanisms responsible for rejection or loss of function should be studied.

#### **4.3.3.2 Studies on viral mobilisation**

The possibility that replication competent and pathogenic endogenous retroviral elements in the xenogeneic cells could be mobilised and rearranged should be addressed also in relevant non-clinical studies.

The possibility of reactivation of other types of human latent viruses (e.g. herpes zoster, Epstein-Barr virus and cytomegalovirus) should also be investigated when appropriate.

*In vitro* studies on viral mobilisation after xenogeneic transplantation to human tissue should be performed. The necessity for *in vivo* studies should be addressed.

## **4.4. CLINICAL DEVELOPMENT**

### **4.4.1. General aspects**

The clinical development of xenogeneic cell-based products should involve initially patients with serious or life-threatening disease for whom adequately safe and effective alternative therapies are not available, or where there is a potential for a clinically significant benefit.

The relevant CHMP guidelines for clinical trials, including the Guideline on cell-based medicinal products (EMA/CHMP/410896/2006) should be taken into account.

Additionally, the following aspects of the clinical application of xenogeneic cell-based medicinal product should be considered:

- Concomitant treatments should be carefully documented, including the monitoring procedures for therapeutic effects and adverse events.
- Particular attention should be paid to the ethical issues linked to the ethnic/cultural background of the recipients.
- Interventional techniques should be clearly described. Feasibility of repeated administration of xenogeneic cell-based medicinal product and the consequences should be evaluated. Justification for the techniques is required, particularly if the techniques are new to clinical practice.
- Recipients of a xenogeneic medicinal product should be informed that exclusion criteria for blood, cell/tissue and organ donation apply to them. In addition, female recipients should be advised not to breast feed.

#### **4.4.2. Pharmacodynamics**

In general, the pharmacodynamic endpoints for xenogeneic and allogeneic cell-based medicinal product should be the same. The pharmacodynamic/physiological functionality of the xenogeneic cell-based medicinal product in the recipients should be evaluated taking into account common risk factors .

#### **4.4.3. Pharmacokinetics**

The distribution, proliferation and survival of the xenogeneic cells and their interaction with the tissues/organs of the recipient need to be characterised. Putative ectopic engraftment of animal cells in non-target human tissues should be addressed and the possibility of cell fusion should be considered. The methods of measurements and duration of assessment should be justified.

#### **4.4.4. Dose finding studies**

In general, the dose finding studies for xenogeneic cell therapy should be performed according to the same principles as those applied for human allogeneic cell-based medicinal products (EMA/CHMP/410896/2006).

#### **4.4.5. Clinical efficacy studies**

The principles of the confirmatory clinical trials are the same as for other medicinal products, especially allogeneic cell-based medicinal products (EMA/CHMP/410896/2006) including a randomised clinical trial design.

#### **4.4.6. Clinical safety and Public Health implications**

The safety assessment should mainly address the risks of the recipients, but may also involve some measures that concern those in close contact with the recipients, health care professionals and the general public.

Safety issues arising from immune rejection, immunosuppression, and breakdown of immunisation devices should be considered. The development of late complications, such as cancer and opportunistic infections should be taken in account in the planning of long-term follow up of the patients. In general, the safety studies of concomitant treatments in the context of xenogeneic cell-based therapy should be similar to those applied for the human allogeneic cell therapy. However, xenogeneic cell-based therapy may require immunosuppressive regimens and other concomitant medications that have not been used in routine treatment setting. In such cases, the relevant additional data should be provided.

The risk of clinical failure due to a different sensitivity of the xenogeneic cells to human medicines (taken by the recipient) as well as to the life style of recipients and to common population illnesses (e.g. cold, flu) should be evaluated.

The risk of transmission of infection in the course of treatment with a xenogeneic cell-based medicinal product represents one of the most important issues to be considered. The concomitant use of heavy immunosuppression may alter the normal pattern of potential infections.

The infections may be caused by human pathogens, pathogens originating from the xenogeneic cells or by pathogen that could emerge through recombination. There may be a significant delay of clinical manifestations of infection and the symptoms of an infection may be atypical, e.g. organ dysfunction, or hyperacute, foudroyant forms. Thus, when the aetiology of a recipient's post-treatment illness or reasons for a failure of the xenogeneic cell therapy remain unclear, appropriate testing should be conducted.

A detailed plan for screening, treating and control of unexpected infectious diseases should be in place. This plan should be followed and updated throughout the clinical development and during the post-marketing phase.

The administration of xenogeneic cell-based medicinal product should be performed in facilities that provide the necessary containment and procedures to ensure the appropriate care and follow up of the patients, and the necessary safety measures for all close contacts during the initial period after treatment. A system to follow-up close contacts of the recipients and health care professionals may be required (see also pharmacovigilance section) when relevant.

The appropriate follow up schedule may be presented in the Summary of Product Characteristics (SPC)

#### **4.5. PHARMACOVIGILANCE AND RISK MANAGEMENT PLAN**

The special characteristics of xenogeneic cell-based medicinal product should be considered, taking into account the different levels of risks associated with each individual product and the proposed therapeutic use. The requirements of a Risk Management Plan have to be considered also in the light of relevant national and EU legislation. For xenogeneic cell-based medicinal product there are numerous adventitious agents (viral, bacterial, parasitical infections and infestations) that need to be considered. Also malignancies and other potential long term adverse effects, the associated medical devices and biomaterials have to be taken into account. The Guideline on Safety and Efficacy Follow-up - Risk Management of Advanced Therapy Medicinal Products should be consulted (EMA/149995/2008).

##### **4.5.1 Surveillance plan**

The pharmacovigilance plan should contain a specific surveillance plan. The plan should enable rapid identification of epidemiologically significant links, and should provide data for the assessment of long-term safety of xenogeneic cell-based therapy. The extent and duration of monitoring of the treated individuals should be justified. For in vivo xenogeneic cell-based medicinal products it may be necessary to follow-up all recipients. It should be ensured that the medical records of the recipient contain all relevant information for both safety and maintenance of efficacy profiling. The information provided in the health records should be specified in the RMP.

An adequate laboratory testing program with suitable, validated methods should be in place to enable screening in case of adverse events. The active screening programme requires the collection and archiving of appropriate body fluids (blood, plasma, urine etc). These materials should be kept under adequate storage conditions for retrospective testing in the case of a diagnosed infection or a suspected infection within an acceptable time period after administration of the xenogeneic medicinal product. The MAH has to take provisions for the surveillance system, that all samples and records will be maintained or appropriately transferred to anyone agreed with the competent authority in the event that the establishment ceases operation.

The plan may have to be modified according to new scientific information on the infectious agents and their epidemiology. It has to be defined prior to marketing authorisation which tests should be performed on a regular basis. It may be acceptable that certain tests will only be performed when clinically indicated (e.g. in the case of a suspected transmission of an infectious agents).

An efficient surveillance system allowing for the retrieval and linkage of the observation with the clinical records, the biological specimens and the source material, manufacturing, storage and distribution should be in place and ready for use prior to marketing authorisation.

##### **4.5.2. Surveillance of close contacts and health care professionals involved in therapy with xenogeneic cell-based medicinal products**

It is important to provide adequate information about possible risks to close contacts and health care professionals involved in xenogeneic cell-based therapy. It is not always feasible or necessary to monitor close contacts and health care providers on a routine basis for infectious diseases related to xenogeneic cell therapy. However, the events that would trigger the surveillance of the close contacts must be identified in advance. The system becomes operative if the recipient is infected with xenogeneic agents and a risk of transmission cannot be excluded for close contacts and health care providers. All efforts should be made to adequately inform close contacts if transmission of infectious

agents cannot be excluded. It may be, in rare instances, necessary to collect blood samples of close contacts (e.g. family) prior to the procedure and store for retrospective testing. The MAH should be responsible for providing comprehensive information specific for the product to health care workers in order to ensure proper handling of the product, the treatment procedure and the follow up.