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REGULATORY ASPECTS OF CLINICAL AND RISK MANAGEMENT STUDY OF XENOTRANSPLANTATION IN US AND EUROPE

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ABSTRACT

The current shortage in human organs has made xenotransplantation a potential source of organ transplant in humans. Xenotransplantation attracted interest from regulatory authorities, particularly after the demonstration of pig-to-human transmission of porcine endogenous retrovirus (1996). This added to the risk of a product, resulting in a Guidance of the US Food and Drug Administration (2003). The European Medicines Agency issued a Guideline on xenogeneic cell therapy products (2009). These addressees the full flow chart starting with the clinical protocol review and health records of clinical trials, also risk related to non human primates and surveillance plan for minimizing the risks. This article presents an overview of the regulatory framework with the special focus on the clinical study regulation and risk management programme in US and Europe.

INTRODUCTION:

Human Transplantation is a relatively new field of medicine that is now facing the significant challenge. Because of its clinical success, the need for these procedures exceeds the availability of donor organs. Each year Fewer than half the people on transplant waiting lists receive organ transplant. Approximately 10 people die each day waiting for organs to become available. Even if all potential donors elect to donate, the supply of human organ donation will continue to fall short of the need. One solution along with pharmaceutical and biotechnology companies is investigating to end this acute shortage is "Xenotransplantation". Xenotransplantation is the transplantation of living cells, tissues or organs from one species to another. Such cells, tissues or organs are called Xenografts or Xenotransplants. Xenotransplantation to humans is defined as any procedure that involves direct transplantation, implantation or infusion of live cells, tissues or organs from a non human animal source. This term is also applied when human body fluids, cells, tissues or organ are used that had come into contact with live non human animal cells, tissues or organs and might be contaminated by an infectious agent from another species.

CLINICAL STUDY REGULATIONS IN US: [2]

Clinical trials are conducted for safety and efficacy studies. The basic

knowledge and clinical experience with Xenotransplantation is limited but current issues may be resolved.

Clinical protocol review:

Sponsors are responsible for ensuring these reviews as appropriate by local review bodies, including Institutional review board (IRB), Institutional Animal care and use committees (IACU) and Institutional Biosafety committees (IBC). The human subject protection issues traditionally addressed by local IRBs, institutional review of xenotransplantation clinical trial protocols are also address:

- The potential risks of infection for the contact populations (including health care providers, family members, friends, and the community at large)
- Source animal husbandry (e.g; screening program, animal quarantine)
- Suitability of the proposal to address issues related to human and veterinary infectious diseases (including virology, laboratory diagnostics, epidemiology, and risk assessment).

Design of Clinical Study:

- Due to the potentially serious public health risks, limit the xenotransplantation to patients for whom the following can be demonstrated:
- A serious or life-threatening disease for which adequately safe and effective alternative therapies are not available, except when very high assurance of safety can be demonstrated.
- The potential for a clinically significant improvement with increased quality of life following the procedure.
- The ability to comply with public health measures, including long-term monitoring.

Risk/Benefit Analysis Ratio:

The lack of other therapeutic options and the severity of disease may raise the benefit-to-risk ratio for some individuals. However, consideration and evaluation of risks and benefits of xenotransplantation is addressing both recipient and public health concerns. Infectious disease is among the potential risks both to the recipient and to the public posed by the use of xenotransplantation products. Uncertainties associated with any potential recipient and public health consequences of each of the events are described and examined. Transmission of microbial agents from xenotransplantation products could lead to systemic disease like infection or failure of the xenotransplantation product in the recipient. Transmission of infectious agents could result in outbreaks of zoonotic disease, silent transmission of latent viruses, or emergence of new strains of pathogens. The widespread horizontal or vertical transmission of new pathogens is possible before the pathogens are recognized (e.g., Human Immunodeficiency Virus). The possibilities and uncertainties associated with any other types of adverse events that could have potential, significant recipient or public health impact, arising from the xenotransplantation product are described and examined. Any immunological risks, including rejection of the live xenogeneic cells, tissues, or organs are described.

Health Records and Data Management:

The recipient's medical record contains information on the recipient's health and all xenotransplantation-related information, including procedures, a description of the xenotransplantation product, and any xenotransplantation product-related adverse events are ensured. In addition, an appropriate

tracking system for all recipients of their xenotransplantation products are developed and use this tracking information to facilitate notification in the case of a serious adverse event related to a xenotransplantation product. Information is collected when events occur, such as a xenotransplantation procedure or an adverse event, and at the time of clinical follow-up examinations. Reporting forms are uniform and include information relevant to the recipient. The information to be collected and tracked includes, at a minimum, the following:

1. Facility information - Sponsors should record information regarding their animal facilities, manufacturing facilities, and clinical centres associated with each source animal, xenotransplantation product, and recipient.
2. Recipient information - Recipients by code number or other identifier are identified to link the recipient to relevant information in the tracking system.
3. Procedure information – Information about each xenotransplantation procedure are recorded.
   - recipient identifiers
   - the date of the procedure
   - the clinical centre where the procedure was performed
   - the physician or investigator who performed the procedure
   - the clinical indication for the xenotransplantation procedure
   - medications and therapies administered at the time of the procedure
   - a description of the xenotransplantation products
   - identification of the animal source
   - animal facilities for each animal source
   - xenotransplantation product manufacturing facilities
   - Other pertinent clinical information.
3. Adverse Event Reports - A sponsor must record adverse events and report the events to FDA, consistent to existing regulation (21 CFR 312.32). Sponsors should keep records of each event.
4. Recipient clinical follow-up examinations - Clinical status information for recipients of xenotransplantation products are collected.

   This information is included but is not limited to:
   - the date of the clinical follow-up examination
   - the location of the clinical follow-up examination
   - the status of the xenotransplantation product in the recipient
   - any new significant co-morbidities
   - Any hospitalizations since the recipient's last clinical follow-up examination.
5. Animal Health Events - Animal facilities should record animal health events. These events include but are not limited to:
   - breaks in environmental barriers of the secured animal facility
   - disease outbreaks
   - Sudden, unexplained or unexpected animal deaths.
6. Recipient Death Reports - Sponsors should maintain death reports on recipients. This information is including recipient identifying information, the date of death, and the cause of death. Death certificate and autopsy information are recorded, if available.

Informed Consent: General Comments: The informed consent document must include the standard contents (21 CFR Part 50). **Specific Issues**: Within the general outline of the informed consent document, certain specific issues regarding recipients are addressed.

Categories of potential pathogens resulting from xenotransplantation (examples and availability of validated microbiological assays)

Common Human Pathogens of Allotransplant Recipients	(EBV, CMV, herpes simplex virus, varicella zoster virus, Apergillus species, *Listeria monocytogenes*, mycobacterial species, *Pneumocystis jirovecii*) Specific microbiological assays are generally available
Traditional Zoonoses	well-characterized clinical syndromes of humans (*Toxoplasma gondii)* Specific microbiological assays are generally available
Species-specific agents	organisms *generally* thought to be incapable of causing infection outside the xenograft (e.g., porcine CMV) Some specific microbiological assays are available; few standardized assays available for use in humans
Potential pathogens	Organisms of broad "host range" which *may* spread beyond the xenograft (adenovirus) Some specific microbiological assays are available for use in humans, may not be standardized for porcine strains
Unknown pathogens	Organisms not known to be human pathogens, not known to be present in the source animals, or for which clinical syndromes and microbiologic assays are poorly described or unknown New pathogenicity within the new host, while not known to be present or pathogenic (e.g., protozoa or retroviruses)

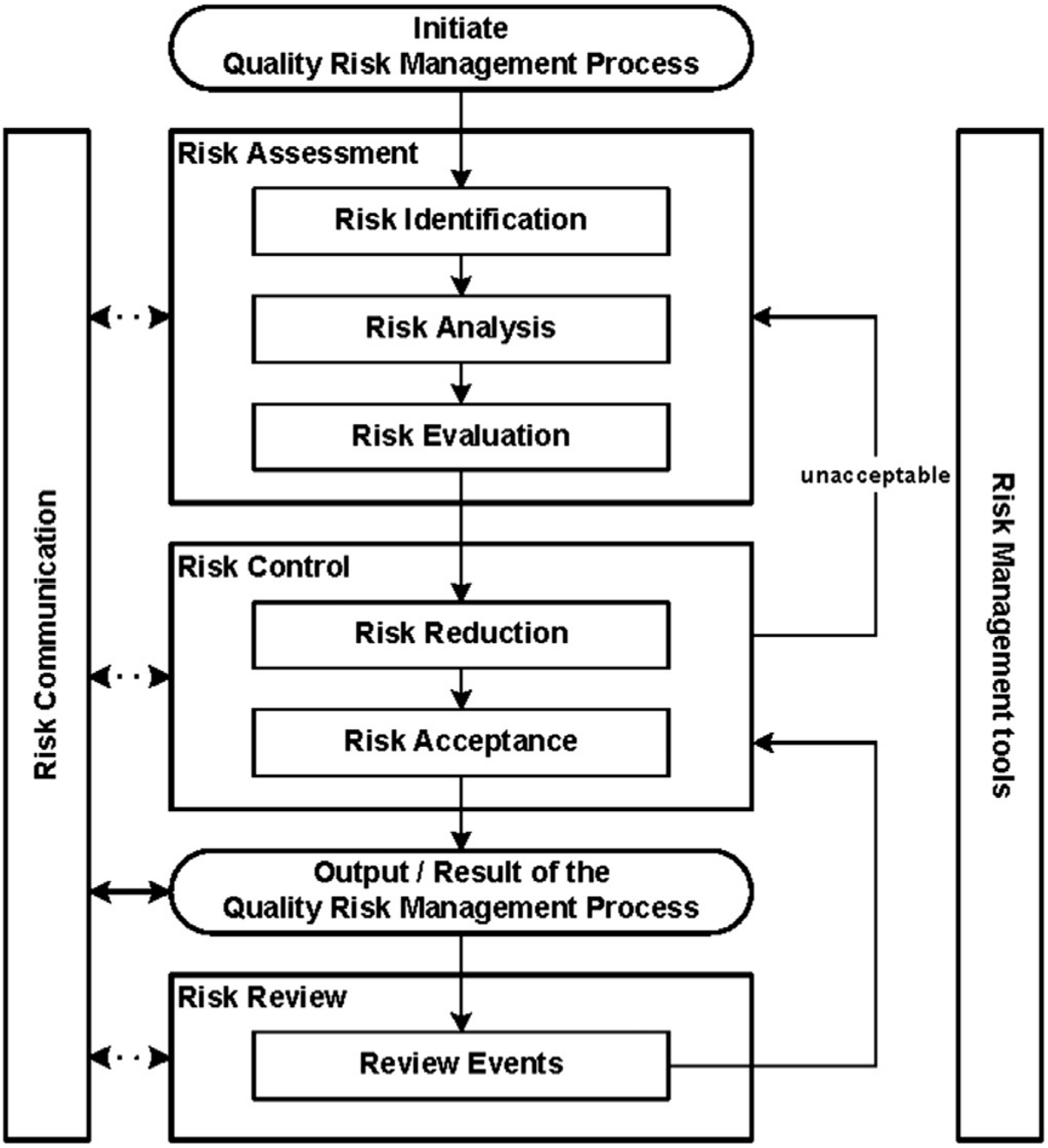

Figure: A scheme of risk analysis and management

a. Participation in the Study:

b. Risks to the Recipient and his/her Intimate Contacts:

c. Potential Benefits:

d. Alternative Treatments

e. Possible Consequences and Subsequent Treatment Options:

RISK MANAGEMENT PROGRAMME IN US: [3, 4, 5]

Risks Associated with Nonhuman Primate Xenotransplantation:

Xenotransplantation raises a major public health problem: how to balance the potential promise of this emerging technology to reduce the shortage of live cells, tissues, and organs currently available for transplantation with the risk of potential transmission of infectious agents to the patient, his/her close contacts, and the public at large. Experience with human-to-human transplantation has demonstrated the transmissibility of infectious agents from donor to recipient through transplants (e.g., Human Immunodeficiency Virus (HIV), Hepatitis B Virus, and Hepatitis C Virus).

- Xenotransplantation may facilitate inter-species spread of infectious agents from animals to the human host through several mechanisms:

  a) Surgery damages the normal anatomical barriers to infection such as skin, membranes, etc.

  b) Transplant recipients are usually induced immunosuppressed to facilitate graft survival

  c) Patients' underlying disease, such as AIDS or diabetes, may compromise their immune response to infectious agents. Nonhuman primates shelter several known infectious agents which are potential human pathogens and which can produce clinically latent infections and/or persistent infections. These agents include a variety of retroviruses (e.g., Simian Immunodeficiency Virus [SIV], Simian Foamy Viruses [SFV], Simian T Lymphotropic Viruses [STLV], Baboon Endogenous Retrovirus, and/or Simian Type D Retroviruses) and a variety of herpes viruses (e.g., herpesvirus papio, baboon cytomegalovirus [CMV], and SA-8). These agents are often found at high rates in nonhuman primate colonies.

Categories of potential pathogens resulting from xenotransplantation (examples and availability of validated microbiological assays)

Surveillance plan:

An approach will be needed for the evaluation of xenograft recipients. Investigations will be based on a number of categories that reflect differing urgency and implications for clinical trials of xenotransplantation:

1. Routine surveillance of healthy source animals (screening).

2. Routine surveillance of recipients (screening) pre- and post-transplantation {e.g., microbiologic testing for specific agents (e.g., PERV by serology and/or nucleic acid testing [NAT] as controlled by the monitoring protocol such as every 3 months for 5 years) following the transplant, then at appropriate intervals for the life of the xenograft recipient}. Microbial assays that are performed in the absence of clinical symptoms or other irregularities may provide epidemiologic data useful in the assessment of safety in clinical trials.

3. Routine evaluation of social and sexual contacts of xenograft recipients, possibly including household pets.

4. Evaluation of infectious syndromes (e.g., fever of unknown origin [FUO], leukocytosis, leukopenia, graft dysfunction, pneumonia, hepatitis) in xenograft recipients, including,

   - Exclusion of syndromes commonly associated with allotransplantation (e.g., CMV) or due to immunosuppressive drugs or of technical and surgical adverse events.

   - Evaluation of PERV infection by serologic and NAT testing.

   - Assessment of other recipients of xenografts derived from the same herd or source of swine.

- Evaluation of sexual and close social contacts of recipient after identification of infectious syndrome in the recipient.
- Investigation of recipients for unknown pathogens or organisms not previously associated with clinical syndromes in humans.

Investigations would require testing of the source animal (archived specimens and/or herd) and recipient including, but not limited to: Cultures and examination of blood, urine, sputum, stool, cerebrospinal fluids for bacteria, fungi, viruses, parasites.

1. Testing for common human pathogens of immunocompromised hosts depending on the clinical syndrome (CMV, Epstein–Barr virus [EBV], *Cryptococcus neoformans*, mycobacteria, *Nocardia* species)
2. Specific porcine pathogen testing (PERV, porcine cytomegalovirus [PCMV], porcine lymphotropic herpesvirus [PLHV], circovirus, hepatitis E virus)
3. Cocultures on permissive cell lines.

Techniques for surveillance:

1. Surveillance for novel pathogens
2. Assays related to PERV

Review Committee:

The United States Public Health Service (PHS) agencies including the FDA, NIH, CDC, and HRSA have worked together to address:
a) The infectious disease risks posed by xenotransplantation;
b) The baseline safety measures for the procurement, screening, and use of xenografts
c) The clinical care of xenograft recipients within the U.S.

CLINICAL STUDY REGULATIONS IN EUROPE: [6, 7]

- The clinical development of xenogeneic cell-based products is involving 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.
  - Additionally, the following aspects of the clinical application of xenogeneic cell-based medicinal product should be considered: Associated treatments are carefully documented, including the monitoring procedures for therapeutic effects and adverse events.
  - Particular attention is paid to the ethical issues linked to the ethnic/cultural background of the recipients.
  - Interventional techniques are 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 are informed that exclusion criteria for blood, cell/tissue and organ donation apply to them. In addition, female recipients are advised not to breast feed.

Claims and Patient selection:

The use of xenogeneic cell therapy may be attractive because of limited availability of human cells and comparatively reduced risk of immune rejection compared with solid organ xenograft. There are at least 3 types of possible claims: Temporary, Bridging and Extracorpeal use, Treatment of last resort, treatment where other alternatives available. Because of potentially serious public health risk arising from transmission of infectious agent, Xenogeneic cell therapy is limited to

patients with the serious or life threatening disease for whom adequately safe and effective alternative therapies are not available and where there is potential for clinically significant benefit.

Pharmacodynamics:

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

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

Dose finding studies: The quantity of cells required to achieve the indented clinical endpoints is determined. The methods of qualification and dosage calculations are justified.

Concomitant treatment: A number of measures may be used to enhance safety and efficacy. These may include immunosuppressive agents, anticoagulants, antiviral agents and even vaccination. Concomitant treatment schedule is tested repeatedly including monitoring procedures for therapeutic effects and adverse effects.

Pivotal Clinical Trial: The design of clinical trial is appropriate for the clinical condition in question. The other considerations are: Informed consent and counselling: This will require detailed information on risk and alternatives, the need for the long term follow up with regular efficacy and safety assessment, archiving of plasma and tissue samples for future analysis, possible access of recipient's medical records by public health agencies.

- The duration and schedule for follow up safety and efficacy assessment is justified.
- Adoption of optimal technique for manipulation and administration of Xenogeneic cells.
- Interventional techniques are clearly justified. Feasibility of repeat procedure and the consequences is evaluated. Justifications for the techniques are required specially if the techniques are new to clinical practise.
- The sponsor should commit to updating the recipients with new information on risk; benefit and need for additional treatment as part of long term follow up.
- Public health implication

Health Records: Health records should be ensured that the recipients' medical records contain all relevant information on recipients health including all screening test results, all adverse events and all results of retrospective testing as well as relevant xenogeneic cell therapy related information including procedure, product description including information of the source animal. A tracking system should be implemented. Additional information including clinical examination and laboratory testing as well as additional information on source animal should be collected in case of adverse events.

Health records should include:

Product information: Animal source, manufacturing facilities, clinical centres, xenogeneic cell therapy product identifier, MAH contacts Recipient Information and Procedure information:

- Recipient identifier, date of procedure, procedure decription

4. Medical History and Clinical status of the recipient prior to procedure
5. Medical information at each follow up:
    - Medications and therapies of the recipient, clinical information on rejection reaction, infections, hospitalization or inter current condition.
6. Adverse event Reporter

RISK MANAGEMENT PROGRAMME IN EUROPE: [6, 7, 8]

Risk Associated with Xenotransplantation:

Xenotransplantation poses a risk of accidently transmitting infection and disease to humans, not only for the recipient but also for the whole human population. It falls into the category of hazard where, although the risk is probably low and the benefit to individuals undoubtedly substantial, the public consequences could be tragic. There are numerous pathogens present in non-human primates, and the genetic relatedness of primates with humans suggests that their micro-organisms may be relatively easily transmitted and adapt to their new human host and spread. While all kinds of infectious agents such as bacteria, viruses, parasites, protozoa, fungi and others may be transmitted viruses, is the major concern. Several exogenous retroviruses common in humans (such as HIV-1, HIV-2, HTLV-1, and HLTV-2) originate from non-human primate viruses. In addition, there may still be unknown transmissible agents in non-human primates. For these reasons the Working Group of the Council of Europe on Xenotransplantation concluded that non-human primates should not be used as source animals (Council of Europe, 2000). However, the use of pigs also shelters a risk for introducing infection and disease into humans.

Categories of viral infections that theoretically may be transmitted to humans, each of which has its own risk level, are listed below:

1. Zoonoses, such as influenza A, rabies and others.
2. Possible or potential zoonoses, such as encephalomyocarditis, porcine endogenous retroviruses (PERVs), and others,
3. Common pig viruses that normally do no infect man, such as classical swine fever, cytomegalovirus, parvovirus, and others,
4. Viruses that normally do not infect pigs, but have incidentally been reported to infect pigs, which include lymphocytic choriomeningitis, Hantaan virus, and others
5. New viruses that may arise due to recombination of retroviral human and porcine sequences, or due to the formation of pseudotypes, i.e. a hybrid virus carrying the genome of one virus and the envelope of another

Surveillance plan for possible risk: Zoonoses, both known and unknown may be difficult to recognise without special surveillance methods. There should be a plan to control possible infections.

- **Establishment of a special surveillance system:** According to national and European surveillance system there is a need of applying new tools and methods.
- The surveillance system needs to be fully operational and has to start prior to exposure of patients to the products irrespective whether in clinical trials.
- Tracking of patients and close contacts for potential development of infections that may present public health hazards is considered to be of inherent importance. The establishment of surveillance system shall ensure full traceability of medicinal products, documentation of manufacturing process of individual batches of raw materials used and animal records. Information from all relevant sources should be integrated.

- The system should enable rapid identification of epidemiological significant common features among recipients and provide data for the assessment of long term safety of xenogeneic cell therapy.

1. **Key elements of the surveillance to be considered in a risk management plan**:

A. Clinical surveillance of individuals should be in place in order to monitor for clinical diseases.
B. Laboratory testing of recipients is a powerful increase to clinical monitoring.
C. Monitoring data of all recipients via registries is deemed necessary.
D. Biological specimen archives ensure the ability to investigate future adverse events.
E. Data should be registered in a database for identification of risk signals and common features among recipients and reviewed on a regular basis.

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 viable 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.

CONCLUSION:

Xenotransplantation is tremendous field for fulfilling the demanding necessities of shortage of organs by transplanting animal organs in to humans. Regulatory aspects of xenotransplantation products are complex, but do not block product development therefore stringent regulations for Xenotransplantation are necessary. In this study it is observed that countries like United States and Europe having stringent regulations to be followed. In this way, it will be possible to make new xenotransplantation products through development to a product on the market, to meet the medical need of all those patients with end-stage organ dysfunction waiting for a xenotransplantation product.

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REFERENCES:

1. Xenotransplantation: The and Risks of Special Organ Transplantation https://www.bio.org/.../xenotransplantation-benefits-and-risks-special-organ-transplantation
2. USFDA, “Guidance for industry: Source animal, product, preclinical and clinical issues concerning the use of Xenotransplantation products in Humans” http://www.fda.gov/BiologicsBloodVa

ccines/GuidanceComplianceRegulatory Information/Guidances/default.htm.

3. USFDA, "Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans"https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/xenotransplantation/ucm092866.pdf
4. Jay AF, Linda S and Yasuhiro T, "Xenotransplantation- associated infectious risk: a WHO consultation." *Official Journal of the International Xenotransplantation Association,* **2012,** 19(2), 72-81.
5. Roumiana SB, Thomas MF, and Louisa EC, "Infectious Disease issues in Xenotransplantation." *Clin Microbiol Rev, **2001,*** 14(1), 1-14
6. European Medical agency, "Xenotransplantation Regulations,"http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003893.pdf
7. EMEA, " Points to be consider on Xenogeneic cell therapy medicinal products"http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003893.pdf
8. Jay and Yasuhiro, "Xenotransplantation- associated infectious risk: a WHO consultation." *Official Journal of the International Xenotransplantation Association,* **2012,** 19(2), 72-81.