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**Table of Contents**

	Page
1. INTRODUCTION.....	1
2. CURRENT DIRECTIONS IN XENOTRANSPLANTATION RESEARCH AND TECHNOLOGY DEVELOPMENT.....	2
3. XENOZOONOTIC DISEASE RISK AND PREVENTION ISSUES: MANAGEMENT OF XENOZOONOTIC RISK.....	2
3.1 Identify the infectious agents concerned.....	3
3.2 Prevent the transmission of xenozoonoses through xenografts.....	3
3.3 Evaluate and manage xenozoonoses occurring in Xenotransplantation recipients.....	3
3.4 Prevent and manage secondary transmission of xenozoonotic infections.....	4
4. ETHICAL AND SOCIAL CONSIDERATIONS.....	5
4.1 Potential impact on attitudes towards human organ donation and the availability of organs for transplantation.....	5
4.2 Cultural, societal and recipient attitudes towards Xenotransplantation.....	5
4.3 Consent and consensus: human rights and community interest issues.....	6
4.4 Source animal care and use.....	6
5. DEVELOPING GUIDELINES, POLICIES, AND REGULATIONS ON XENOTRANSPLANTATION: EXAMPLES OF NATIONAL APPROACHES.....	7
5.1 Canada.....	7
5.2 France.....	7
5.3 Switzerland.....	8
5.4 The United Kingdom.....	8
5.5 The United States.....	9
6. DEVELOPING GUIDELINES, POLICIES, AND REGULATIONS ON	

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XENOTRANSPLANTATION: EXAMPLE OF AN INTERNATIONAL APPROACH, THE COUNCIL OF EUROPE.....	9
7. CONCLUSIONS.....	10
8. RECOMMENDATIONS.....	11
8.1 Recommendations to Member States.....	11
8.1.1 Mechanisms and procedures for the promotion of individual and public health and safety.....	11
8.1.2 Research on zoonoses.....	11
8.1.3 Quality assurance of cell, tissue and organ production.....	12
8.1.4 Source animal health assurance.....	12
8.1.5 Risk assessment: monitoring and surveillance of recipients and immediate contacts (including health care providers).....	12
8.1.6 Counselling of xenotransplant recipients.....	13
8.1.7 Counselling of immediate contacts of xenotransplant recipients (including health care providers).....	13
8.1.8 Registries and archives.....	13
8.1.9 Ethical considerations.....	13
8.1.10 Efficacy of Xenotransplantation.....	14
8.1.11 Equitable access.....	14
8.1.12 Animal welfare.....	14
8.1.13 Xenotransplant review boards.....	14
8.1.14 International cooperation.....	15
8.2 Recommendations to WHO.....	16
ANNEX 1: List of participants.....	17

## 1. INTRODUCTION

Xenotransplantation, the transplantation of animal cells, tissues or organs into humans, is a current area of clinical research which may one day become part of medical practice. Advances are being made in the development of strategies to overcome the technical problems to its application. These may ultimately lead to the use of this technology as an alternative or additional approach for alleviating the global shortage of human tissues and organs for allotransplantation. Xenotransplantation may also offer the prospect of being a treatment for diseases with no other effective therapeutic intervention, such as refractory Parkinson's disease or Huntington's disease, or an additional therapeutic approach to conditions such as diabetes mellitus. Although the technology is being developed in the industrialized world, its use, if proven safe and efficacious, may eventually be available globally. Xenotransplantation has the potential to contribute to the alleviation of suffering and improvement of human health worldwide.

On the other hand, the development and implementation of this technology requires careful consideration. Xenotransplantation could have adverse consequences such as the cross-species transmission of animal infectious diseases to human xenograft recipients, their contacts and the wider human population. These diseases, which are called zoonoses, would expand zoonoses (infections transmitted from animals to humans under natural conditions) to include infections not currently recognized as transmitted via animals or those in which xenotransplantation alters pathogenicity. Since both the potential advantages and risks cross national boundaries, xenotransplantation is a public health issue which must be dealt with at both the national and international levels. If national approaches to xenotransplantation research and possible use are to be viable, they will require complementary international activities and initiatives.

In addition, due attention must be paid to ethical, social and religious values and perceptions, which will have a major influence on the ultimate acceptance or rejection of xenotransplantation as an implementable biomedical technology. There is a need for discussing the ethical issues raised, recognizing that the responses may differ from one country or region to another.

## **2. CURRENT DIRECTIONS IN XENOTRANSPLANTATION RESEARCH AND TECHNOLOGY DEVELOPMENT**

Transplantation has gained general acceptance as a practice for treating patients with a variety of medical conditions. The human donation of transplantable organs and tissues, however, has not kept pace with demand. As a result, additional and alternative sources are being sought. One possibility currently under investigation is the use of animals as a source of cells, tissues and organs. (Such animals are referred to as “source animals” in these discussions.)

Current research is exploring ways of overcoming the immunological problems associated with xenotransplant rejection. Results are being applied to the development and refinement of strategies that modify the recipient's immune system, and to the use of genetically engineered animals as sources of cells, tissues and organs. Cloning technology is being explored as a means of producing cells, tissues and source animals suitable for xenotransplantation.

The entry of xenotransplantation into the modern clinical arena is being approached in a cautious manner, step by step. The first steps, cellular xenografts and extracorporeal use of xenogenetic organs, are being undertaken through limited clinical trials. There is preliminary evidence that porcine cellular grafts may endure in human recipients. Subsequent steps will probably involve the use of xenogenetic organs as temporary transplants or bridges. Bridges by themselves will not solve the problem of organ shortages, but can serve the secondary purpose of providing additional vital information on the remaining immunological and biological problems to be addressed. Only afterwards, with further refinements resulting from continued research and data analysis, may xenotransplantation be considered as a full supplement or viable alternative to allotransplantation.

## **3. XENOZOONOTIC DISEASE RISK AND PREVENTION ISSUES**

One concern raised about xenotransplantation is the risk of inadvertent transmission of infectious agents into xenotransplant recipients and subsequent secondary transmission of infections to the wider human population. This risk is an important obstacle to the use of this technology. The potential for secondary transmission of infections makes the risk of xenozoonoses a global issue. Management of this risk requires reliable strategies for prevention, detection and containment. WHO has produced a detailed guidance document on the prevention and management of xenozoonoses (WHO/EMC/ZOO/98.1).

The management of xenozoonotic risk should focus on devising and carrying out activities which:

- C identify the infectious agents concerned;
- C prevent transmission of xenozoonoses from xenografts;
- C evaluate and manage any xenozoonoses occurring in xenotransplantation recipients;
- C prevent or manage secondary transmission of xenozoonotic infections.

### **3.1 Identify the infectious agents concerned**

A number of infectious agents which can cause disease in humans and which could be transmitted via xenotransplantation are already known, such as rabies or toxoplasmosis. It must be assumed that the capacity of many other recognized infectious agents of animals to infect xenotransplant recipients and be secondarily transmitted to other humans remains incompletely defined and should therefore be the subject of further research. It must also be assumed that there are other infectious agents of animals that are not yet recognized, but which could pose a risk of infection or disease for xenotransplant recipients and the wider human population. This implies that there is a need for continuous development and refinement of diagnostic capabilities for identifying potentially new infectious agents of animals. Because of the risk of such agents, risk management systems need to be developed. They must be frequently reassessed in the light of new knowledge to ensure that agent detection and management procedures remain appropriate for each xenotransplant application, and conform to acceptable standards of safety.

### **3.2 Prevent the transmission of zoonoses through xenografts**

Preventing infections in source animals is the key to preventing their subsequent transmission into xenotransplant recipients. It is likely that the potential for zoonoses will be significantly reduced by practices which keep animal colonies free of infectious agents known or thought to be relevant to xenotransplantation. These colonies should be maintained as specified pathogen free. Prevention of disease will also depend on the aseptic procurement, processing, delivery and transplantation of xenografts into human recipients. Training of staff in proper animal husbandry and xenograft harvesting techniques will be an important element in all xenotransplant programmes.

### **3.3 Evaluate and manage zoonoses occurring in xenotransplantation recipients**

Before conducting a xenotransplant, the potential recipient should be screened for various infectious agents which might:

- C pose a risk to the recipient after xenotransplantation;
- C infect the xenograft;
- C impair the accurate interpretation of tests for infectious agents after xenotransplantation.

To complement this screening, appropriate biological samples from the potential recipient should be archived to allow for future retrospective analysis as determined necessary.

After transplantation, evaluation of the recipient for zoonoses should be carried out on a regular basis and in response to the occurrence of illness. There should be routine clinical surveillance, periodic analysis and archiving of appropriate biological samples for zoonotic agent antigen or antibody detection, agent isolation, and molecular diagnostic assays. These evaluations may need to be conducted throughout the life of the recipient. Examinations, screening and archiving should all be organized to facilitate recipient health care, and to aid in subsequent epidemiological investigations should they become necessary.

The importance of promoting research to develop accurate, reliable and simple diagnostic tests cannot be overemphasized. It will be essential to have the ability to identify accurately the species of origin of agents found in xenotransplant recipients. It will also be critical to have the ability to

diagnose such latent infectious agents as retroviruses or herpes viruses and to detect as yet unknown, unrecognized or newly emerging agents.

In addition, archives of appropriate biological samples from source animals should be maintained to enable retrospective investigations and analyses of suspected zoonotic events. Procedures for archiving samples should be designed to ensure consistency, adequate preservation and accessibility of the sampled material at national and international levels.

National and international registries of xenotransplant source animals, animal colonies and recipients should be kept. Such registries will allow epidemiological monitoring of xenograft recipient populations for evidence of zoonotic events.

Compatibility of national archive and registry procedures will be required to allow for a ready comparison of information, epidemiological analysis, and international communication. Access to these archives and registries should be restricted to protect the privacy and dignity of individual recipients while allowing directed investigations necessary for the common good.

### **3.4 Prevent or manage secondary transmission of zoonotic infections**

Some infectious agents may pose a risk to public health because they may be transmitted from infected xenotransplant recipients to other humans. Thus, from a public health perspective, attention must be given not only to xenograft recipients but also to their contacts.

Patient counselling should be conducted before transplantation, and should include specific discussions on the impact xenotransplantation may have on recipients and their relationships with other people. There is a need for frank and open discussions with prospective recipients and their immediate contacts about the risks of infection and disease, and about possible prevention measures. After transplantation, when deemed necessary, recipients should agree to use physical and/or procedural barriers aimed at preventing agent transmission. Recipients should adapt their activities and behaviour post-xenotransplant to the requirements of public safety.

Before working with xenotransplant recipients, health care providers should be informed of the potential risk of zoonoses and advised of all precautionary steps they should take or procedures they should follow in the performance of their duties. Occupational health and hospital protocols should be worked out for each xenotransplantation application.

The national and international registries of recipients recommended above (2.13) will be useful tools for monitoring and protecting community health through epidemiological surveillance.

## **4. ETHICAL AND SOCIAL CONSIDERATIONS**

Several ethical issues are raised by research on xenotransplantation and its potential use. They can be categorized as those concerning:



- C its impact on allotransplant donation and availability;
- C personal and societal perceptions of the appropriateness and acceptability of the technology and its attendant risks;
- C issues of informed consent, protection of human rights and community interests including access to information;
- C animal species selection, animal welfare and use, and the genetic engineering of animals, including cloning.

#### **4.1 Potential impact on attitudes towards human organ donation and the availability of organs for transplantation**

Continuous improvements in allotransplantation survival rates have resulted in an increasing gap between the demand for allotransplantation and the number of organs and tissues available by human donation. Xenotransplantation may eventually become a method of alleviating this shortage, but it is unlikely in the near future at least, to eliminate the need for human organ donation. Therefore, efforts should continue to encourage human organ donation.

In many parts of the world the shortage of human organ and tissue donations is exacerbated by insufficient national capacity to provide chronic and expensive treatments such as dialysis. Technical and economic constraints sometimes dictate the need to perform life-saving transplantation procedures sooner rather than later to ensure the optimal management of eligible patients. As one alternative to human organ and tissue donation, xenotransplantation may become a practical treatment modality, if reasonable standards of safety and efficacy can be ensured. It could also help enhance equity of access in those countries where chronic institutional health care is unavailable or non affordable, and where allotransplantation is not accessible because of insufficient levels of donation. In the long term, because of the ability to plan and coordinate transplantations, xenotransplantation may become an economical alternative to human organ or tissue transplantation.

#### **4.2 Cultural, societal and recipient attitudes towards xenotransplantation**

The various cultural and societal responses to xenotransplantation are difficult to predict. The appropriateness or acceptability of xenotransplantation will differ between cultures and societies and may change over time. Xenotransplantation may raise specific issues such as the appropriateness of the use of animals as sources of cells, tissues or organs for transplantation into humans, the implications of genetic engineering for animals and humans, and the potential psychological issues which may arise from the presence of animal cells, tissues, or organs in a recipient.

Cultural norms, attitudes, and belief systems shape the perceptions of societies and individuals. A major influence on people's attitude towards xenotransplantation will be their perception of the scientific validity and medical justification for the procedure. Regulatory mechanisms for ensuring accountability, protection of public interests, and the minimization of risk will probably be required. Equitable access to the technology's benefits may also be required. Scientists, health professionals and other partners involved, such as religious leaders and the media, can play an important role in providing public information and fostering debate on this technology's potential safety, efficacy and desirability. Together, these factors will help to determine the acceptability or unacceptability of xenotransplantation.

#### **4.3 Consent and consensus: human rights and community rights issues**

Basic principles of biomedical ethics such as beneficence, non-maleficence, autonomy and justice are also applicable to xenotransplantation as a therapeutic modality. They should, for example, be applied to both the recipient and the community in a balanced manner. Both the patient and the community have the right to expect that the principle of precaution is exercised. It should be made clear that a balance of risks, not a total absence of risk is expected. Within this context therefore, non-maleficence to both the recipient and the community demands that rigour be exercised in searching for potential transmission of xenozoonoses and other clinical complications.

Exceptions to the rights of patients are usually anticipated in law when it is deemed necessary for public good. This often means limitations which apply for reasons of public order, public health and other persons' human rights. The guiding rule in such exceptions is always that patients can be subjected only to such limitations as are compatible with human rights instruments and in accordance with a procedure prescribed by law.

In general, the informed consent of a patient is considered a prerequisite for any medical intervention. When the consent of a legal representative is required, however, recipients must nevertheless be involved in the decision-making process to the fullest extent which their capacity allows.

The regulatory balance between recipient and community interests will vary between nations and societies, and will reflect legal, ethical and cultural norms. If appropriate, laws may have to be modified or written to establish a regulatory infrastructure for this technology. International cooperation will be necessary to promote the compatibility of the national regulatory frameworks applicable to xenotransplantation and its related infectious disease management activities.

#### **4.4 Source animal care and use**

If a country authorizes xenotransplantation, it must determine which animal species should be used for this purpose, and how animal welfare principles might be integrated into this proposed usage.

Pigs have been considered as xenotransplant source animals because of their comparable organ size and general anatomic similarities to humans. The species is also currently favoured because of the existent knowledge of its diseases and husbandry requirements. Non-human primates have been considered because of their phylogenetic and therefore expected immunological and physiological similarities to humans. However, animal welfare concerns, zoonosis transmission risks, and animal conservation issues have been greater in the case of non-human primates, and therefore have discouraged the use of these animals as source animals. The ultimate selection of a source animal species should be based on the above considerations and, in particular, the need to use animals that are as free as possible from potentially infectious agents and diseases.

Xenotransplant source animals, regardless of species, should be treated in a manner consistent with animal welfare principles. They should not be subjected to undue pain or distress, nor be used indiscriminately or wastefully. The Council for International Organizations of Medical Sciences (CIOMS), in *Principles for Biomedical Research Involving Animals* (1985) outline some principles that may be used to govern the use of animals for xenotransplantation, but each country will need to develop its own approach to dealing with issues relating to animal welfare.

If a country decides to use genetically engineered source animals for xenotransplantation, the development and use of such animals should be conducted in a manner compatible with animal welfare principles.

## **5. DEVELOPING GUIDELINES, POLICIES, AND REGULATIONS ON XENOTRANSPLANTATION: EXAMPLES OF NATIONAL APPROACHES**

### **5.1 Canada**

In Canada, pre-clinical xenotransplantation research is occurring. A Standards Based Risk Management (SBRM) regulatory framework is being developed for organ and tissue transplantation. A key component of the SBRM approach is the Canadian General Standard (CGS) on Safety of Organs and Tissues for Transplantation and the development of specific standard subsets for individual organ and tissue groups - including xenotransplantation - which will be recognized under the National Standards System of Canada. SBRM - including methods to verify compliance, adverse event reporting and patient registries - will be administered through Health Canada with both stakeholder and provincial participation. SBRM addresses the need to continually update and revise practices as science evolves. It can complement international activities and facilitate harmonization of regulatory approaches to xenotransplantation surveillance and practice.

The legislative basis for regulation of xenotransplantation is the Canadian Food and Drugs Act. At present, Health Canada views the proposed standards for xenotransplantation as guidance for the planning and development of xenotransplantation trials only. A National Forum for public and professional opinion development and decision making on the future clinical use of xenotransplantation was held on November 6-8, 1997. A report of the Forum will be released early in 1998, and future steps will be announced at that time.

### **5.2 France**

The Etablissement français des Greffes has formed an expert committee on xenotransplantation for reviewing and analysing developments in xenotransplantation technology. In anticipation of the potential implementation of xenotransplantation in France, this expert committee is in the process of developing guidance documents on various aspects of safety assurance. A health safety law is anticipated in the near future which will include a specific chapter regarding the safety and evaluation of xenotransplantation clinical research and practice. The ethical aspects of xenotransplantation are presently under scrutiny by the National Advisory Ethics Committee.

### **5.3 Switzerland**

The Swiss Government has proposed a paragraph which will be the constitutional basis for a new law regulating the transplantation of organs, tissues and cells of human and animal origin. The official commentary to this paragraph points out the risks involved in xenotransplantation, as well as the need to consider the ethical issues raised by this technology. On condition that the aforementioned paragraph is accepted by the Swiss people in a referendum (probably in 1998), the

federal authorities will formulate a law concerning transplantation medicine. This law will also cover xenotransplantation.

In 1997, an MP from the Socialist Party called for a moratorium on xenotransplantation. The parliament rejected this proposal, but accepted an alternative proposal calling for the regulation of xenotransplantation including an approval procedure for this technology.

Following earlier political activities concerning xenotransplantation, the Programme Technology Assessment of the Swiss Science Council launched a study in 1996 to assess the social, ethical and economic aspects, as well as the risks, of xenotransplantation. This project should be finished in the spring of 1998.

#### **5.4 The United Kingdom**

The UK Government commenced work on xenotransplantation when it established the Advisory Group on the Ethics of Xenotransplantation, under the Chairmanship of Professor Ian Kennedy in March 1996. Their report, *Animal Tissue into Humans*, was published in January 1997. Its main conclusions were that xenotransplantation could be acceptable provided that certain criteria were met and that there should be some national committee to oversee developments. However, the main conclusion was that key or pre-conditions (around safety and efficacy) had not yet been met and that it was not therefore appropriate to allow xenotransplantation in humans. In response to this report, the Government established the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) to regulate the development and implementation of xenotransplantation. Proposals for xenotransplantation may be submitted to the UKXIRA, which will advise on whether they are acceptable. Proposals must also be considered by Research Ethics Committees and comply with other relevant legislation on genetically modified organisms and the use of animals in scientific procedures.

An independent UK body, the Nuffield Council on Bioethics also published a report on xenotransplantation: *Animal to Human Transplants: the ethics of xenotransplantation* in March 1996. That document reviewed the technical and ethical issues surrounding xenotransplantation, and recommended that "the development of xenotransplantation should continue subject to rigorous regulation to ensure protection for potential human recipients and care for animal welfare". It recommended that the clinical application of xenotransplantation should not proceed until preclinical safety and efficacy issues were fully addressed.

#### **5.5 The United States**

The Department of Health and Human Services, through its Public Health Service agencies (National Institutes of Health, Centers for Disease Control and Prevention, the Health Resources and Services Administration, and the Food and Drug Administration), has formed a national level Committee on Xenotransplantation. A central goal of the Committee, as expressed in the *DRAFT PHS Guideline on Infectious Disease Issues in Xenotransplantation*, (September 1996) is to delineate baseline safety requirements for the procurement, screening, and use of xenografts, as well

as the clinical care and follow up of xenograft recipients, in order to minimize the risks associated with xenotransplantation due to known and emerging infectious agents.

Also under development are a Pilot National Xenotransplantation Registry Database (NXRD). A biologic specimen archive(s) system, a national xenotransplantation advisory body, and a mechanism for regulatory oversight.

Currently there are two levels of review and approval requisite to assess whether appropriate safeguards, are in place before a xenotransplantation clinical trial can proceed. At the local level, a proposal must be reviewed by three institutional committees: the Institutional Review Board, Institutional Biosafety Committee, and the Institutional Animal Care and Use Committee. These review each protocol to assess individual risk/benefits, community safety, and animal use, respectively. Since xenotransplants are considered Biologics, they are subject to regulation nationally by the FDA under the US Public Health Service Act and the US Federal Food, Drug and Cosmetic Act. This requires that an Investigational New Drug application be submitted to the FDA for review and approval before an investigator can proceed with any xenotransplantation clinical trial.

A series of public workshops on cross-species transplantation is underway exploring the infectious disease issues surrounding xenotransplantation, and presenting the evolving US public health policy on xenotransplantation implementation and regulation.

## **6. DEVELOPING GUIDELINES, POLICIES, AND REGULATIONS ON XENOTRANSPLANTATION: EXAMPLE OF AN INTERNATIONAL APPROACH, THE COUNCIL OF EUROPE**

On 20 September 1997, the Council of Europe's Committee of Ministers to Member States on Xenotransplantation, adopted its Recommendation No. R(97) 15. This recommendation encourages Council of Europe members to consider that xenotransplantation may become a practised therapeutic intervention in the near future, and that Governments of Member States might wish to adopt common and coordinated approaches to this technology's oversight and regulation with the view towards minimizing the risk of transmitting known or unknown diseases and infections to either the human or animal population. Specifically, it recommends that States consider establishing mechanisms for the registration and regulation of xenotransplantation associated basic research and clinical trials; the origin, care and use of xenotransplant source animals; xenotransplant programmes; and the long term follow-up and review of xenograft recipients and source animals.

Also, the Council of Europe, through its Steering Committee on Bioethics, Working Party on Organ Transplantation, is actively reviewing xenotransplantation as it relates to issues of human rights and bioethics. This Committee has given specific mention to the need to address animal welfare and public safety concerns.

## **7. CONCLUSIONS**

A fundamental goal of the World Health Organization is to encourage the development of safe, effective, ethical, and accessible methods for improving human health worldwide. In light of this overall goal, the Consultation on Xenotransplantation reached the following conclusions:

- C Research and development in xenotransplantation technology are proceeding at a very rapid pace. Careful and timely consideration must be given to the possibility of infectious disease transmission and to the ethical implications of the development and potential use of this technology.
- C The practice of xenotransplantation carries with it an unquantifiable risk of zoonotic infection and disease. Measures are required to minimize risk and maximize safety in the potential use of this technology.
- C The implications of this technology are not solely biomedical. It also raises philosophical issues, including questions of ethical, social, cultural and religious acceptability. Public acceptance should not be assumed. Psychological, cultural, and societal concerns call for accurate information and frank public debate.
- C The use of transgenic, cloned, or otherwise genetically engineered animals as sources of cells, tissues or organs may be considered acceptable as long as the dignity and identity of humans are respected, human health is protected, and animal welfare is adequately taken into account.
- C Consideration should be given to the economics of xenotransplantation. Realistic estimates are needed of the cost of developing, applying and transferring the technology and of providing whatever infrastructure and institutional support may be needed. The relative costs and benefits of the technology to the recipient and to the health care system will also have to be measured with respect to the societal and economic environments concerned.
- C National policies should be developed to promote safety, efficacy, equity and ethical practice.
- C International cooperation and coordination are needed to help promote safety, efficacy and equitable access to the technology. They are also needed to protect human dignity and individual rights together with community interests.

## **8. RECOMMENDATIONS**

The recommendations below recognize the need for further research on the safety and efficacy of xenotransplantation, and the need to take into account the diversity of social, cultural, and religious values, as well as the relevant national and international professional, ethical, and legal norms. The Consultation recognizes that there are different opinions about xenotransplantation research, and different ways of approaching it. These recommendations are not meant to encourage or discourage early clinical trials, but rather to call attention to the issues that need to be taken into account by countries considering the adoption of this technology.

The Consultation offers these recommendations as starting points to help Member States and other interested parties deal with xenotransplantation issues, and work out their own policies, regulations and guidance for the safe and ethical use of this technology. They also attempt to provide a framework which can contribute to public health and safety at both the national and international level.

## **8.1 Recommendations to Member States**

Member States should consider including the following elements in their approaches to xenotransplantation:

### **8.1.1 Mechanisms and procedures for the promotion of individual and public health and safety**

Mechanisms should be designed and introduced to maximize individual and public health and safety, including a framework for the detection, prevention and management of xenozoonoses. Specifically:

#### **8.1.2 Research on xenozoonoses**

Support should be given to basic and clinical research on xenozoonoses, and to the development and refinement of laboratory and other capabilities aimed at the prevention, detection, diagnosis, and treatment of xenozoonotic infections and diseases.

#### **8.1.3 Quality assurance of cell, tissue and organ production**

Comprehensive mechanisms and protocols should be established and implemented for the quality assurance of xenotransplant cell, tissue, and organ production. They should be directed towards:

- C identifying and developing source animals which will provide cells, tissues, or organs of the best possible quality;
- C eliminating xenozoonotic agents from source animals;
- C preventing source animal exposure to xenotransplant relevant infectious agents;

- C encouraging the development and use of comprehensive health surveillance programmes for source animals;
- C encouraging the clinical investigation of any health problems that occur in source animals and the development and use of appropriate diagnostic procedures;
- C promoting the safe delivery of cells, tissues and organs to the xenotransplant recipient.

#### **8.1.4 Source animal health assurance**

Part of the quality assurance process outlined above is the development of a total health assurance process for source animals. It is recommended that source animals be assessed for the presence of potentially relevant infectious agents as part of this process. Consideration should be given to:

- C the relevance of infectious agents to the context of specific protocols and usages;
- C the use of criteria for developing xeno-zoonotic agent exclusion lists;
- C the enlistment of multidisciplinary expertise for the development and evaluation of animal health assurance protocols;
- C the need for continuous review of the entire animal health programme based on up-to-date scientific knowledge and research.

#### **8.1.5 Risk assessment: monitoring and surveillance of recipients and immediate contacts (including health care providers)**

Comprehensive patient and contact infectious disease risk assessments strategies, including surveillance and monitoring methods and protocols should be established and periodically reviewed to:

- C reduce xeno-zoonotic risk to the general population by preventing and managing xeno-zoonotic transmission events;
- C expand the epidemiological knowledge of xeno-zoonotic risk.

These methods and protocols should be practical and clinically feasible. They should be considered long-term, if not life-long. Potential recipients must be informed of the surveillance constraints and obligations inherent in proceeding with the xenotransplantation, and their consent to participate must be sought.

If a xeno-zoonotic event occurs, management responses should be kept proportionate to the risk involved. Mechanisms should be established to protect recipients from unreasonable restriction of their individual rights and freedoms while recognizing the responsibility to protect community health and safety.

#### **8.1.6 Counselling of xenotransplant recipients**

Mechanisms and protocols should be established for counselling potential xenotransplantation recipients on the need to:

- C cope with physical, psychological and emotional effects of the xenotransplant on themselves and their contacts;



- C refrain from donating whole blood, blood components, source plasma, source leukocytes and other body fluids, tissues or parts to other humans;
- C use barrier precautions to prevent the transmission of potentially latent and unrecognized infection through intimate contact;
- C recognize that intercourse and breastfeeding may lead to xenozoonosis transmission;
- C participate in long-term and possibly life-long monitoring and surveillance procedures.

#### **8.1.7 Counselling of immediate contacts of xenotransplant recipients (including health care providers)**

Mechanisms and protocols should be established for counselling family members of xenotransplant recipients, as well as other immediate contacts and health care providers on:

- C the psychological and emotional questions and concerns arising from contact with xenotransplant recipients;
- C appropriate barrier precautions to prevent potential exposure to infectious agents associated with xenotransplantation;
- C participate in risk assessment investigations, which may include monitoring and surveillance procedures.

#### **8.1.8 Registries and archives**

Registries and archives of tissues and body fluids of both recipients and source animals should be kept as resources for the purposes of epidemiological investigation. They should be designed and managed so as to protect the privacy and dignity of individual recipients while facilitating investigations necessary for the common good.

#### **8.1.9 Ethical considerations**

Efforts must be made to promote informed public consideration of the desirability or appropriateness of xenotransplantation, taking into account the specific social, economic, cultural, and religious beliefs and legal norms in the country concerned.

#### **8.1.10 Efficacy of xenotransplantation**

If xenotransplantation applications are to proceed, they must conform to acceptable standards of ethics and good clinical and scientific practices. This should require the demonstration of:

- C the existence of an adequate scientific base to justify moving to clinical trials;
- C adequate training of xenotransplantation personnel and other health care providers;
- C the availability and use of appropriate patient care facilities and health care infrastructure.

#### **8.1.11 Equitable access**

Procedures and mechanisms should be established for assuring equitable and just implementation of the technology both at national and international levels. Their functions should include:

- C adherence to basic principles of respect for the rights and dignity of humans;
- C equitable access to scientific and technical information about xenotransplantation and to its benefits;
- C periodic assessment of procedures to ensure equitable access to the technology.

#### **8.1.12 Animal welfare**

Mechanisms and procedures should be established or strengthened to ensure animal welfare. This should be aimed at:

- C minimizing potentially adverse effects to the animals produced as sources of cells, tissues or organs for xenotransplantation,
- C overseeing genetic engineering to ensure that animals do not lose their identity as members of their species.

#### **8.1.13 Xenotransplant review boards**

Xenotransplant review boards, advisory or supervisory bodies should be established. They should have multidisciplinary expertise in areas such as xenotransplantation technology, infectious diseases, preventive medicine, public health principles, anthropology, ethics, law, and human rights, and should promote:

- C the frequent and timely review of national xenotransplantation policies, regulations, and guidance in the light of current knowledge and understanding;
- C the protection of xenograft recipients from unreasonable or unjustifiable limitations on their individual rights and freedoms;
- C international communication and cooperation on xenotransplantation issues;
- C the establishment and maintenance of archives and registries on both recipients and source animals.

#### **8.1.14 International cooperation**

International cooperation and coordination are needed to help promote the safety and efficacy of xenotransplantation as well as equity of access to the technology. International cooperation is also needed to ensure that xenotransplantation is developed in conformity with accepted ethical and legal standards based on the need to respect human dignity and individual rights together with community interests. International cooperation should therefore promote:

- C the gathering and dissemination of information on xenotransplantation research and development;
- C the development of adequate and compatible national registries and databases:
  - to facilitate the global assessment of the technology,

- to coordinate surveillance and response in case of adverse or unusual events,
  - to support communication and cooperation between national, regional, and international organizations and societies;
- C the establishment of cooperative links between countries to facilitate bilateral or multilateral research and surveillance on zoonoses, including zoonotic event notification procedures;
- C the establishment of international registries of recipients and source animals.

## 8.2 Recommendations to WHO

The Consultation recommends that WHO should:

- C distribute this document and enhance awareness of xenotransplantation developments among all Member States;
- C provide guidance on the issues raised by xenotransplantation technology and its potential use;
- C facilitate national, regional and global discussion on issues related to xenotransplantation, including the need to prevent and manage zoonoses;
- C promote public debate on the ethical issues raised by xenotransplantation in different cultural, religious and social environments;
- C support the development of measures which maximize safety, efficacy and adherence to ethical standards in the conduct of xenotransplantation;
- C provide technical expertise and guidance to support the development of national and international xenotransplantation archives and registries;
- C foster compatibility and cooperation between national programmes and systems to promote the international exchange of information and aid in the investigation of zoonotic infection and disease;
- C help to set up an international notification system for xenotransplant-associated diseases;
- C establish mechanisms such as a WHO panel of experts to provide technical support in carrying out these recommendations and promoting public dialogue and education.