COUNCIL OF EUROPE CONSEIL DE L'EUROPE

Strasbourg, 19 June 2003
[bioethics/textes publics/CDB-INF/2003/
INF(2003)12e xeno ER]

CDBI/INF (2003) 12

STEERING COMMITTEE ON BIOETHICS
(CDBI)

EUROPEAN HEALTH COMMITTEE
(CDSP)

Explanatory Report to Recommendation Rec (2003)10 of the Committee of Ministers to member states on xenotransplantation

SUMMARY OF CONTENTS

Introduction

The transplantation from humans to humans of organs, tissues and cells has been recognised as a successful therapeutic solution to several previously incurable diseases relating to heart, liver, lung and kidney disorders. Furthermore, this procedure could potentially address other unmet medical needs such as incurable neurological diseases (Parkinson's and Alzheimer's disease), paraplegia due to spinal cord lesions and pancreatic islet or beta cell transplants for treatment of diabetes.

At the moment, most organ transplants are derived from deceased human donors. However, the needs exceed many times the supply and a number of patients continue to die on waiting lists. Because of this acute shortage, some scientists have studied the possibility of transplanting organs originating from animals to human persons, which is referred to as xenotransplantation.

However, because of the particular nature of these animal organs and since there are certain dangers in xenotransplantation which do not exist, or are less clear, in allotransplantation (human to human), additional precautions are necessary for this activity. This is especially the case with respect to immunological difficulties, the potential threat of animal pathogens in humans and intricate issues related to the quality of xenotransplants, animal welfare[1] and the ethical acceptability of using animals for this purpose. Though some of these difficulties could eventually be overcome, there is still insufficient knowledge concerning the potential risks involved in most of the procedures, such as the transmission of animal pathogens in human beings.

Because of these risks, the Recommendation on Xenotransplantation asserts the need for very stringent and demanding conditions whereby no animal to human xenotransplantation should be carried out in a member state that does not provide regulation for such a procedure. This condition is extremely important to protect patients, public health and the animals used. Therefore, if a State does not provide regulation for animal to human xenotransplantation, it should not be allowed to proceed with any clinical intervention be it for research or for any other reason.

During the three years of the Working Party, competing biotechnologies, such as stem cell technology, have been emerging which could potentially address the needs for cell and tissue (but not for complete organ) transplantations. At the moment, it is uncertain whether these new discoveries will have similar or even better prospects than xenotransplantation, particularly with respect to clinical applications.

Drafting of the Recommendation

The Parliamentary Assembly of the Council of Europe, having considered the risks to public health which xenotransplantation could involve asked the Committee of Ministers, on the 29th of January 1999 (Recommendation 1399 (1999) on Xenotransplantation), to initiate a study concerning the different aspects of the relevant issues relating to xenotransplantation taking into account the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (European Treaty Series: ETS - No.164).

The same year, the Committee of Ministers established a Working Party (CDBI/CDSP-XENO) under the joint authority of the Steering Committee on Bioethics (CDBI) and the European Health Committee (CDSP) to evaluate the risks in xenotransplantation and establish appropriate safeguards.

Chaired by Mr. Bart Wijnberg (The Netherlands), the Working Party was composed of Prof. Didier Houssin (Vice-Chair, France), Prof. Annika Tibell (Vice-Chair, Sweden), Prof. Pekka Häyry (Finland), Prof. Karin Ulrichs (Germany), Dr. Marialuisa Lavitrano (Italy), Dr. Dag Sorensen (Norway), Prof. Alexander Tonevitsky (Russian Federation), Dr. Rafael Manez (Spain), Dr. Theodor Weber (Switzerland), Dr. David Cook (United Kingdom), Dr. Maggy Jennings (United Kingdom) and Dr. Line Matthiessen (European Community).

It should be noted that representatives from several non-member states (Prof. Eda Bloom (United States) and Dr. Larry Whitehouse (Canada)) in addition to several organisations ((International Xenotransplantation Association (IXA), OECD, Office International des Epizooties (OIE) and WHO)) were active participants, as observers, in the work. Indeed, it was considered that worldwide cooperation between states was necessary in this field and that the participation of representatives of these non-member states and international

[1] A more detailed discussion of these concerns can be found in the state of the art report on xenotransplantation drafted by the Working Party (CDBI/CDSP-XENO).

organisations would enable the drafting of common standards, especially with respect to protecting public health.

The Working Party finalised a draft Recommendation on xenotransplantation in September 2001. In this Recommendation, the Working Party drafted stringent and careful provisions in order to address the concerns expressed by the Parliamentary Assembly. Accordingly, the text states that no animal to human xenotransplantation can be carried out unless sufficient efficacy and safety has been demonstrated. Furthermore, the Recommendation recognises that the xenotransplantation of cells and tissues is already taking place in a number of countries. Therefore, provisions encouraging international co-operation in public health, including with countries where xenotransplantation is prohibited, are incorporated.

The Recommendation is accompanied by this Explanatory Report drawn up under the responsibility of the Secretary General of the Council of Europe. It takes into account the discussions held in the CDBI and CDSP as well as in the Working Party entrusted with the initial drafting of the Recommendation; it also takes into account the remarks and proposals made by Delegations. The Explanatory Report is not an authoritative interpretation of the Recommendation. Nevertheless, it covers the main issues of the preparatory work and provides information to clarify the object and purpose of the Recommendation and makes the scope of its provisions more comprehensible.

Preamble

Protection and guarantees in the field of biology and medicine are provided by the European Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine. In the specific field of transplantation, complementary protection for patients is also given by the Additional Protocol to the aforementioned Convention concerning Transplantation of Organs and Tissues of Human Origin.

Furthermore, the European Convention for the Protection of Vertebrate Animals used for experimental and other Scientific Purposes guarantees protection for animals involved in investigatory procedures including those used in xenotransplantation.

The Preamble stresses the importance of the 3rd Conference of European Health Ministers convened in Paris in November 1987 dealing with organ transplantation and also takes due regard to the previous work of the Committee of Ministers and the Parliamentary Assembly of the Council of Europe in the field of transplantation and xenotransplantation.

In addition, the Preamble emphasises the importance of considering the work of other national and international organisations relating to xenotransplantation since a communal approach has been recognised as being essential in addressing the relevant issues.

Chapter I – Object, scope and definitions

Article 1 – Object of the Recommendation

1. The aim of the Recommendation is to protect all persons involved in xenotransplantation (patients, close personal contacts and the professional staff involved in xenotransplantation) as well as public health, both in the short term and long term. The provisions also aim to ensure that the welfare of animals used for xenotransplantation is adequately protected. This will include ensuring that source animals are provided with husbandry and care appropriate to their needs and ensuring that the collection of organs, tissues or cells is carried out in a humane manner.

Article 2 – Scope of the Recommendation

2. In the broadest sense, xenotransplantation covers source animals, procurement of organs, tissues and cells, informed consent, surgery and post-operative follow-up and all other activities involving the transplantation of animal parts or human materials which have been in contact with animal parts into human recipients.

Article 3 – Definition

3. Concerning the definition of xenotransplantation:

- The first indent covers the transplantation of parenchymal organs (e.g., kidney, heart, liver, pancreas, lung) and the implantation or infusion of tissues and cells (e.g., skin, bone marrow, blood, pancreatic islets or beta-cells) that have been derived from animals into a human recipient.

- The second indent covers the exposure by a person to human blood or blood constituents that have been in contact with live animal tissues (for example via perfusion), or to human organs, cells or tissues cultured on, or in contact with, live animal cells (regardless of whether they are alive or lethally irradiated but metabolically active), or implanted (stored) in animals.

4. This definition of xenotransplantation includes the transplantation of human stem cell lines and skin cells grown on animal feeder cells but does not include non-living animal products, many of which are regulated as devices (e.g. porcine heart valves), drugs (e.g. porcine insulin) and other biological products (e.g. anti thymocyte globulin, vaccines prepared from animal sources or animal sera used for the culture of human cells).

Chapter II - General provisions

Article 4 – Xenotransplantation – the setting

5. This Article asserts the need for very stringent and demanding conditions whereby no xenotransplantation should be carried out in a member state that does not provide regulation for such a procedure.

6. This regulation should apply the relevant principles of the *Convention on Human Rights and Biomedicine*[2], inter alia those relating to biomedical research. It should also take into account the specific principles and rules relating to transplantation in particular, which are included in the *Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin* (ETS - No. 186) and in *The Transplantation Society Recommendation for Legislation in Transplantation*[3]. On the other hand, recommendations relating to xenotransplantation can be found in the Transplantation Society's *Recommendation on Xenotransplantation*[4], in the WHO's recommendation on the Prevention of Infectious Disease in Xenotransplantation[5], in appropriate US FDA[6] and PHS[7] recommendations and other national recommendations when available[8,9].

---

[2] Council of Europe, 1997, Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (ETS - No. 164).

[3] Additional Protocol to the Convention on Human Rights and Biomedicine concerning Transplantation of Organs and Tissues of Human Origin (ETS - No. 186).
Santiago-Delpin, EA for the Ethics Committee of the Transplantation Society: Guidelines to Assist Authorities in Each Country with regards to Transplantation. The Transplantation Society Bulletin 1997 (ISSN 1070-0676).

[4] Sheil EGR for the Ethics Committee of The Transplantation Society: The Transplantation Society and Xenotransplantation. The Transplantation Society Bulletin 1997 (ISSN 1070-0676).

[5] Xenotransplantation: Guidance on Infectious Disease Prevention and Management. WHO/EMC/ZOO/98.1.

[6] US FDA Draft Guidance for Industry: Source Animal, Product, Pre-clinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans http://www.fda.gov/cber/guidelines.htm

[7] PHS Guideline on Infectious Disease Issues in Xenotransplantation, February 7, 2001.
http://www.fda.gov/cber/gdlns/clinxeno0201.pdf.

[8] Such as the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) report entitled: Infection Risks in Xenotransplantation, Department of Health, April 2001.

[9] The World Medical Association's *Declaration of Helsinki* and its subsequent revisions could be consulted in this regard. World Medical Association Declaration of Helsinki : Ethical Principles for Medical research involving human subjects. Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, the 35th WMA General Assembly, Venice, Italy, October 1983, the 41st WMA General Assembly, Hong Kong, September 1989, the 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

7. Because it is extremely important to ensure that patients, their close personal contacts, public health and the animals used are adequately protected, the term “regulation” in this Article includes the requirement for an “authorisation” to be given by a body officially recognised as competent for this purpose before a xenotransplantation takes place.

8. The regulation should cover all aspects of the proposed procedure such as:

- the collection and maintenance of animal records and the health surveillance plans of the source animals;
- the genetic manipulation of animals or tissues (where relevant);
- the procurement of the xenotransplants and the xenotransplantation procedure;
- the details relating to the qualifications and the necessary scientific and medical expertise of all professional staff involved in xenotransplantation;
- the management of the recipient and his or her close personal contacts;
- the criteria for recipient selection and details of the informed consent document;
- the information programs for the recipient, his or her close personal contacts, the professional staff involved in xenotransplantation and the public;
- the infection control methodologies;
- the immunosuppressive regimens;
- the follow-up time-table and format and the archiving of donor and recipient medical records and specimens.

9. The regulation should also contemplate the possibility of applying constraints such as those mentioned in Article 13.

Article 5 – Xenotransplantation authorisation

10. To begin with, it must be emphasised that xenotransplantation procedures, taking into account their nature, which is still largely experimental, are destined to take place mainly within the framework of biomedical research.

11. The possibility of authorising certain specific procedures, which have been validated for standard care, outside the framework of biomedical research shall only be secondary. An example is procedures using animal cells as a culture medium for human cells with a view to transplantation.

12. In any case, whether it is a question of clinical research or a validated clinical intervention, xenotransplantation procedures must be subject to prior authorisation.

Paragraph 1: Clinical xenotransplantation research

13. To maximise the safety of xenotransplantation in clinical research, each procedure should not only fulfil the general conditions applicable to biomedical research and be authorised by a body officially recognised as competent for this purpose but also comply with specific requirements, namely that the intervention is justified having regard to the risks incurred and the potential level of efficacy and safety for the patient and that, in the light of current scientific knowledge it is highly probable that there is no risk, in particular of infection, for public health. In conformity with Article 12, the results from pre-clinical research should also suggest or, where appropriate, the results from prior clinical research indicate that a clear therapeutic benefit for the xenotransplantation recipient exists. The pre-clinical research must, in the light of current scientific knowledge, have been properly designed to test for all recognisable potential risks, particularly of transmitted infection, and conducted in accordance with internationally accepted scientific standards. Any body authorising clinical xenotransplantation research must be able to assess the extent and quality of the supporting pre-clinical research, or ensure that it has been properly and independently assessed.

14. As long as xenotransplantation remains experimental, last resort procedures should not be considered as possible exceptions to the requirements applicable to clinical research.

Paragraph 2: Xenotransplantation other than in clinical research

15. When a xenotransplantation activity is no longer considered as clinical research, authorisation for this activity should only be given by a body officially recognised as competent for this purpose if there is

adequate evidence that no risks, in particular of infection, to the general population exist and it has an established therapeutic utility. One example of xenotransplantation which cannot be considered research, as it has been in clinical use for over 10 years, is the use of human skin cells grown on mouse feeder cells for the treatment of burns patients. Similar techniques may be used to grow limbal cells to repair damaged corneas. Such techniques are of proven clinical effectiveness but do carry a very small risk of transmission of mouse retrovirus and so should be subject to a risk assessment and proportional patient information and surveillance (see Article 9, paragraph 2).

16. It should be noted that paragraphs 1.a.i. and 2.i. use two different expressions in relation to the absence of risk for public health. Paragraph 1.a.i. uses the expression “highly probable” since indications concerning the absence of such a risk are provided by studies undertaken on animal models; the second paragraph uses the expression “adequate evidence, in accordance with internationally accepted standards” because this evidence is based on research having taken place on human persons. The requirement of a high probability of absence of risks for public health ensures a high level of protection. The wording in paragraph 1.a.i. and 2.i. is meant to imply that, in accordance to the state of the art, there is no foreseeable risk. In science, however, an absolute certainty cannot be given and there is always the possibility of an unknown risk.

Article 6 – Xenotransplantation teams and centres

17. This Article asserts the need for very stringent and demanding conditions whereby no xenotransplantation should be carried out in a member state unless it is undertaken by an accredited team and in an authorised centre.

Indent *a*. (xenotransplantation team):

18. The detection, diagnosis and effective treatment of a recipient subject to an infection in addition to the design and implementation of appropriate measures to limit dissemination of a xenosis, if and when it occurs, are only possible in a well co-ordinated xenotransplantation team. Furthermore, in order to address any possible difficulties arising with the animals this xenotransplantation team should liaise efficiently with the source animal production team.

19. In addition to transplant clinicians and associated staff, the xenotransplantation team should include or have access to an infectious diseases physician with expertise in zoonosis, transplantation and microbiology, a veterinarian with specific expertise in animal husbandry and care issues as well as in infectious diseases of source animals and a hospital epidemiologist/infection control specialist (a team may have more than the indicated number of individuals in order to encompass the necessary expertise). Moreover, the term “appropriately” in indent *a.* also means that other disciplines such as psychology or counselling can be included. Only once the team is composed of experts having recognised qualifications and the necessary skills and experience in all the required disciplines should the team be officially acknowledged as being competent. Several guidelines, in particular in the United States[10] and Canada[11], describe the necessary composition of the xenotransplantation team. Each member state should specify under which conditions a team may be accredited.

20. The xenotransplantation team should be able to fully explore the proposed project with hospital and university administrations with regards to physical resources, the scale of the initial trials and the ensuing clinical program. Moreover, the legal and financial implications of the activity, including reimbursement methods, storage costs of the samples and overall impact on health care expenditures should be considered.

Indent *b*. (xenotransplantation centre):

21. Because xenotransplantation should only take place in centres with relevant experience and equipment, in practice it may mean, particularly in the case of solid organs*,* that only centres already

[10] Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). *Federal register* 1996; 61(185): 49919-32.

[11] Blood, Tissues, Organs and Xenografts Project, Policy Division, Therapeutic Products Programme, Health Protection Branch, Health Canada: Proposed Canadian Standard for Xenotransplantation, Draft 14, July 1999.

authorised to carry out allotransplantations corresponding to the xenotransplantation procedure to be tested could participate in a xenotransplantation (provided that the additional constraints are satisfied).

Chapter III – Protection of Public Health

Article 7 – Public Health protection plan

22. Because there is no room for improvisation in dealing with the risks of xenosis, all provisions and procedures designed to address any events, in particular of infection, possibly related to a xenotransplantation and to react without delay to an event if it occurs, should be thoroughly described in a xenotransplantation plan. These provisions and procedures should include measures to be taken by public authorities to respond to events of transmissible or previously unknown illness possibly related to xenotransplantation. In very exceptional circumstances, such measures might even include the isolation of a patient to prevent any further infections.

23. It should also be noted that, in accordance to Article 32, member states should communicate without delay to national public health authorities of other member states and other concerned states any events, in particular of infection, possibly related to a xenotransplantation, which could compromise public health.

24. Additional information concerning the setting-up of a surveillance framework can be found in the OECD/WHO consultation report on xenotransplantation surveillance[12] and other WHO reports[13,14].

25. The surveillance procedures associated with xenotransplantation can only be effective if they are complied with to the letter. The lifelong constraints which may be imposed on some xenotransplantation recipients and their close personal contacts are such that they may conflict with a number of national and international human rights regulations. This is explained in the discussions with the representatives of the European Court of Human Rights (see Appendix) which states that “[m]any of the rights in the Convention [on Human Rights] were subject to permissible restrictions and involved establishing a proper balance between competing interests.” In particular, the constraints may conflict with the right for one's medical records to remain confidential, the right to mobility and liberty and the right to refuse the constraints which may arise resulting from the xenotransplantation[15].

Article 8 – Collection and storage of biological samples and information

Biological samples

26. In order to ensure traceability and long term monitoring, a number of biological samples should be taken from the source animal used in xenotransplantation and the recipients either for immediate testing or for future reference.

a) With respect to the source animal and source herd, guidelines on the breeding conditions of the source animals include a requirement for appropriate regular sampling to monitor the microbiological status of the herd. This is part of the routine procedures to ensure that xenotransplantation material originates from Specified / Designated / Qualified Pathogen-Free animals.

b) Appropriate blood / tissue samples of the source animal should also be kept indefinitely for future reference. The United States PHS Guideline on Infectious Disease Issues in Xenotransplantation[16]

---

[12] OECD/WHO Consultation on xenotransplantation surveillance:Summary Report, DSTI/BIO(2001)11/FINAL.

[13] Xenotransplantation: Guidance on Infectious Disease Prevention and Management, WHO/EMC/ZOO/98.1.

[14] Report of WHO Consultation on Xenotransplantation, WHO/EMC/ZOO/98.2.

[15] Florencio PS, Caulfield T: Xenotransplantation and Public Health: Identifying the Legal Issues. *Canadian Journal of Public Health* 1999;90(4): 282-4.

[16] Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation. January 19, 2001. http://www.fda.gov/cber/guidelines.htm also see Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). *Federal register* 1996; 61(185): 49919-32.

describes in a specific paragraph "Archives or Source Animal Medical Records and Specimens" the desirable samples and conditions for storage.

c) Provisions should be made for the monitoring of the personnel caring for the animal, the patient, his or her close personal contacts, and the medical and non-medical staff in charge of the patient's care. In relation to the specific xenotransplantation procedure to be tested, the details concerning who is eligible for monitoring, the frequency of such monitoring and the tests to be performed should be determined in advance.

d) In addition, a number of samples should be collected and archived for potential future reference. A proposed patient sampling schedule is given in the United States guideline[17]. According to this document, specimens appropriate to the specific xenotransplant situation, and including systematically blood, plasma and peripheral mononuclear cells, should be collected:

a. every month (or as much apart as possible) before the xenotransplantation,
b. immediately after the xenotransplantation period,
c. approximately 1 month and 6 months post xenotransplantation, then
d. annually for the first 2 years and, finally,
e. every 5 years for the rest of the recipient's life.

27. Specimens of any xenotransplant that is removed (e.g. post-rejection) should be banked. Additionally, it is recommended that specimens of the xenotransplant, serum, blood, white blood cells, and samples of the patient should be stored after his or her death. These specimens should undergo appropriate histological, microbiological and viral assays. Snap-frozen tissue samples, paraffin embedded tissue and tissue suitable for electron microscopy from the xenotransplant and all major organs should be stored.

Health care records

28. The following records should be established and archived:

- an institutional xenotransplantation record;
- a record of hospital acquired infections which may have occurred because of the xenotransplantation;
- individual xenotransplant recipient medical records.

National Registry

29. All countries where xenotransplantation is performed should establish a national registry. Archiving of samples of sera, plasma, leukocytes and tissue of the source animal and recipient should be included in all national guidelines for xenotransplantation.

Article 9 – Follow-up

Paragraph 1: Clinical xenotransplantation research

30. A plan ensuring the traceability and monitoring of recipients, close personal contacts and professional staff involved in xenotransplantation should be set up. This plan should include the collection and storage of information and biological samples from recipients in accordance with Article 8. The existence of this plan is important in order to detect and deal with any infections possibly related to xenotransplantation and any other adverse events. Because of the potentially serious implications of contagion in particular, the plan should also ensure that public authorities are alerted without delay of any events, in particular of infection, possibly related to xenotransplantation.

31. The Article does not define the term "adverse event" as such but this term is meant to imply any adverse incident or occurrence, that is possibly related to the xenotransplantation. An adverse event does not only relate to infections but might also cover incidents such as the appearance of a prion disease. The requirement to communicate information on all such events to the competent body at national level ensures

[17] Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation. January 19, 2001. http://www.fda.gov/cber/guidelines.htm also see Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). Federal register 1996; 61(185): 49919-32.

that those authorities will be able to make a judgment on the possible relevance of the event to public health, rather than such a judgment being made by the research team.

Paragraph 2: Xenotransplantation other than in clinical research

32. Because some xenotransplantation procedures, such as the use of human skin cells grown on animal feeder cells in the treatment of burns victims, have already been used for many years without any evidence of infectious events, the constraints associated with these procedures would only be required insofar as they are necessary and in accordance with the principle of proportionality. It has been recognised that these cells do not pose the same potential risks as some other xenotransplantation interventions and therefore need not be subject to all of the precautions of other xenotransplantation procedures, but that some of them are still appropriate (e.g., recipient notification of the use of mouse cells, initial archiving of recipient samples and passive monitoring, archiving of samples, databasing of recipients...). However, because it is impossible to foresee all possible consequences of an intervention, a plan should also be set up for xenotransplantation other than in clinical research to ensure that public authorities are alerted without delay of any events, in particular of infection, possibly related to such a procedure which could be of relevance to public health.

Article 10 – Precautions relating to the transmission of disease

General considerations

33. It is recognised that one of the key safety issues in xenotransplantation is the risk of xenosis for the recipient with the theoretical possibility of a new, contagious, disease emerging in the human species. Such a scenario is only possible if:

- a potentially pathogen micro-organism is transmitted to the recipient;
- this micro-organism is adapted or adapts to its new environment (the recipient);
- the micro-organism multiplies in the recipient;
- the micro-organism causes a disease;
- inter-human transmission of the micro-organism occurs;
- the (possibly new) micro-organism is also infectious and pathogenic to a section of the population which is large enough to allow its dissemination.

34. Possible actions to minimise such a risk are:

- selection of the source animal species to minimise the risk of xenosis;
- control of the microbiological quality of the xenotransplant;
- prevention of infection in the xenotransplant recipient;
- detection, diagnosis and effective treatment of a possible infection in the recipient;
- limitation of the infection by education and surveillance of the recipient, his or her close personal contacts and any potentially infected person;
- warning without delay in the event that a significant public health hazard is identified, so that appropriate measures can be taken worldwide.

35. Many known micro-organisms which might cause xenosis can be eliminated from the xenotransplant material by the use of appropriate source animal breeding and husbandry conditions, microbiological screening, and organ, cell or tissue procurement procedures. For these reasons, prior to any xenotransplantation authorisation, the breeding and husbandry conditions and procedures, the source animal screening procedures and the xenotransplant procurement and preparation procedures should be thoroughly documented and checked for compliance with appropriate microbiological quality requirements (e.g. qualified pathogen-free). Additionally, a microbiological monitoring and surveillance system encompassing all the stages from the production of the source animals to the final collection of the xenotransplants, should be constantly maintained.

Quality Assurance

A Quality Assurance system should be set up encompassing:

1. All the stages of production of the source animals

36. Breeding source animals devoid of a number of pre-defined micro-organisms (so-called Specified / Designated / Qualified Pathogen-Free animals), and minimising the risk of external contamination of the

source animals or xenotransplants are important. Complex technical recommendations have been or are being elaborated, e.g. in Canada (proposed Canadian Standard for Xenotransplantation[18]), in the United States (PHS Guideline on Infectious Diseases Issues in Xenotransplantation[19]) and in the UK[20].

37. Xenotransplantation source animals should be from lines maintained in biosecure facilities over several generations. The health (specified/designated/QPF) status should be maintained during movement and transport.

38. Pre-clinical screening of source animals should include the most advanced methods for detection of potential infectious agents (bacteria, viruses, prions, parasites and fungi). Microbiological screening should be species-specific and characterise the potential infectious agents for humans. Testing for endogenous retroviruses, persistent viral infections and prions should be considered based on the available technology for such studies.

39. Source animals should come from closed herds or colonies maintained in biosecure facilities under experienced veterinary supervision practising the highest quality of veterinary care. The animals should be screened and qualified as pathogen-free for specific agents as appropriate for the clinical application and be maintained in an environment that minimises exposure to infectious agents and their vectors whilst taking account of their husbandry and care needs as set out in Article 23.

2. The final collection of the xenotransplants

40. Xenotransplanted cells, tissues or organs should be procured with a documented aseptic methodology in facilities meeting the highest surgical standards. Where possible, xenotransplants should be tested repeatedly both before and at the time of xenotransplantation for contamination by infective agents with standard and co-cultivation assays, the latter including appropriate indicator cells and cell lines derived from human peripheral blood mononuclear cells and cells from the xenotransplantation site (e.g. Central Nervous System, bone marrow etc).

Hospital infection control

41. Standard biohazard precautions should be maintained. When the source of a significant illness in a recipient remains unidentified despite standard diagnostic procedures, comprehensive testing of body fluid and tissue samples using validated culture systems, genomic detection methodologies and other advanced techniques should be undertaken. Archiving of acute and convalescent sera and blood cells is also important. An occupational health services program for professional staff involved in xenotransplantation should include an education program together with worker surveillance protocols. Protocols should be established for post-exposure (e.g. needle-stick, splash, mucous membrane exposure) evaluation and management.

42. Should a potential xenogeneic infection related to a clinical episode occur, an epidemiological investigation to assess the potential public health significance of the infection should be initiated without delay in co-ordination with the appropriate public health authorities.

Article 11 – Prohibition relating to the use of non-human primates

Paragraph 1

43. It is presently acknowledged, worldwide, that non-human primates (macaques, baboons, etc.) should not be used as source animals for human xenotransplantation until more information is obtained, allowing a better assessment of the infectious risks. This position is developed in a specific US Food and Drug Administration Guidance Document entitled "*Public Health issues posed by the use of non-human*

[18] Blood, Tissues, Organs and Xenografts Project, Policy Division, Therapeutic Products Programme, Health Protection Branch, Health Canada: Proposed Canadian Standard for Xenotransplantation, Draft 14, July 1999.

[19] Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation. January 19, 2001. http://www.fda.gov/cber/guidelines.htm. See also Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). *Federal register* 1996; 61(185): 49919-32.

[20] Infectious Risks in Xenotransplantation, Department of Health, April 2001.

primate xenografts in humans"[21]. Further reasons to prohibit the use of non-human primates as a source species are the serious welfare implications of maintaining these primates in biosecure conditions together with the wider ethical implications of their use.

44. In Sweden, for example, because of concerns relating to the involvement of non-human primates in xenotransplantation, the Swedish Committee on Xenotransplantation, in their 1999 report, has explicitly banned their use as a source species[22]. Similarly, the proposed Canadian Standard for Xenotransplantation states that despite the greater immunological proximity to humans of primates (absence of preformed antibodies, and therefore, of xenotransplant hyperacute rejection), their use as source animals is not feasible. This is because the phylogenetic proximity of humans to other primates is suspected to increase the probability of xenosis.

Paragraph 2

45. Though non-human primates should not be used as source animals, it should be noted that the literature[23,24] shows that Vero cells (long ago obtained from African Green Monkey kidney cells) have already been used in Switzerland as a vehicle to transfer a gene (interleukin-2) to cancer patients. In addition, there is an *in vitro* fertilization technique used in France in which a Vero cell feeder layer is used[25,26,27]. In this technique, co-cultures of human embryos, particularly with Vero cells, are used mainly in cases of successive failures of implantation. Thus, the use for xenotransplantation of cell lines obtained from non-human primates may be permissible if substantial evidence addressing the infectious disease risks, ethical issues and animal welfare concerns is supplied to the appropriate body (see Article 5), and the said body determines that the evidence is sufficient. However for some types of non-human primates, such as the Great Apes, it is envisaged that no permission for their use as source animals should be given because of serious ethical and animal welfare concerns.

Chapter IV – Protection of patients and close personal contacts

Article 12 – Conditions for patient participation

46. This Article builds on the previous very stringent and demanding conditions whereby no xenotransplantation should be carried out in a member state unless regulation for xenotransplantation activities exists and sufficient efficacy and safety is demonstrated through pre-clinical research.

47. The need for the pre-clinical demonstration of efficacy and safety of the planned therapeutic procedure is not specific to xenotransplantation. These requirements are generally applicable to any new therapeutic procedure being submitted to a clinical evaluation which should establish that the expected benefits outweigh the risks of the procedure.

---

[21] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER): Guidance For Industry: Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans, April 1999.

[22] The Swedish Committee on Xenotransplantation in their 1999 report stated that "*The Committee considers it unacceptable to use non-human primates as source animals, both for ethical and animal protection reasons and also having regard to the risk of infection. However, non-human primates may be, to a limited extent, used as recipient animals during the pre-clinical research phase.*"
Swedish Committee on Xenotransplantation: From one species to another - transplantation from animals to humans. *Swedish Government Official Report* No 1999:120, 1999.

[23] Jantscheff et al, Gene therapy with cytokine-transfected xenogenic cells (Vero-IL-2) in patients with metastatic solid tumors: mechanism(s) of elimination of the transgene-carrying cells. *Cancer Immunology and Immunotherapy* 48:321-330, 1999.

[24] Rochlitz et al, Gene therapy study of cytokine-transfected xenogeneic cells (Vero-interleukin-2) in patients with metastatic solid tumors. *Cancer Gene Therapy* 6:271-281, 1999.

[25] Veiga A, Torello MJ, Menezo Y, Busquets A, Sarrias O, Coroleu B, Barri PN.Use of co-culture of human embryos on Vero cells to improve clinical implantation rate. *Hum Reprod*. 1999 Dec;14 Suppl 2:112-20.

[26] Lapree-Delage G, Volante M, Frydman R, Chaouat G. Interleukin-6 levels in co-culture of human in vitro fertilization embryos with Vero cells are not predictive of future successful development. *Am J Reprod Immunol*. 1999 Feb;41(2):164-7.

[27] Guerin JF, Nicollet B; Interest of co-cultures for embryos obtained by in-vitro fertilization: a French collaborative study. *Hum. Reprod* 1997 May;12(5):1043-6

48. This principle is stated in the European Convention on Human Rights and Biomedicine of the Council of Europe (ETS - No. 164) which states in Chapter V (Scientific research), Article 16, indents i. and ii., that: *"Research on a person may only be undertaken if (i) there is no alternative of comparable effectiveness to research on humans and (ii) the risks which may be incurred by that person are not disproportionate to the potential benefits of the research"*.

49. The objective of pre-clinical research is to quantify, as far as possible, the expected benefits as well as the potential risks to the subject in such a way that the physicians in charge of the patients, the ethics committees and the patients themselves are in a position to make a decision which is as rational as possible. The expected benefits should be carefully weighed against the potential risks, whether quantifiable or not (i.e. a given risk can be foreseeable though not quantifiable), because the nature and level of acceptable risks will depend on the nature and magnitude of the expected benefits.

Specific aspects relating to xenotransplantation

50. In the above key statement of the European Convention on Human Rights and Biomedicine, it is generally considered that the potential benefits of the clinical research may assist either the research participant or other persons (e.g. future patients), or both, but that any risks may only concern the research participant.

51. However, in the field of xenotransplantation, another dimension has to be considered in the decision making process, namely the potential risks to persons other than the patient being treated. These potential risks are mainly of an infectious nature and are, at present, not adequately quantified. They concern (a) the close personal contacts of the xenotransplant recipient and (b) the population at large, with the theoretical possibility of a new disease emerging as a consequence of xenotransplantation. Such a scenario may only occur if a transmitted micro-organism becomes capable of causing a human disease (although there could be a long latency between infection and disease symptoms). Therefore, no xenotransplantation activity should be carried out unless there is adequate evidence, in accordance with internationally accepted scientific standards, that no risks, in particular of infection, to the general population exist.

Therapeutic results expectations

52. The pre-clinical evaluation of efficacy and safety of the proposed xenotransplantation should be addressed separately. However, it is emphasised that any decision to proceed or not with a given xenotransplantation should be based on the evaluation not only of efficacy and safety, but also on a thorough evaluation of the acceptability of a certain level of potential risks, both to the patients and to others, given the level of expected benefits to the patients of the planned study.

Indent i.: Absence of appropriate alternatives

53. Xenotransplantation should not take place if other therapeutic procedures of comparable effectiveness are available for the patient. Indeed, in view of the risk involved in any xenotransplantation, there is no justification for using this procedure if there is another appropriate way of bringing the same benefit to the recipient, such as "conventional" treatment, or tissues of human origin, cultured tissues or tissues transplanted from the recipient. When an appropriate organ or tissue of human origin (allotransplantation) becomes essential to a patient, the shortage of such elements could justify having recourse to xenotransplantation if all other conditions are fulfilled.

54. For patients with acute organ failure, it is often difficult to obtain a suitable allotransplant. Xenotransplantation may in this case provide the best available therapy. The xenotransplant could then either be a permanent solution or be performed as a bridging procedure until a human transplant becomes available.

55. In case of non life-saving procedures, such as renal transplantation, xenotransplants might increase the number of organs available for transplantation and may possibly also increase the transplantation possibilities of patients that are highly sensitised against human tissue and have developed antibodies to the majority of human HLA-antigens.

56. Some diseases causing organ failure are likely to re-occur in the transplanted human organ. The use of a xenotransplant may in some cases reduce this risk since so-called species-specific disease resistance may exist.

57. Xenotransplantation has also been suggested for diseases that are only rarely treated by allotransplantation. Attempts to treat these diseases may use, for example, neuronal cells from fetal tissue which must be procured from the fetus during a very specific developmental stage. In some countries, the use of human fetal material has been explored while in others this is not considered to be acceptable. Besides the ethical problems, the aborted tissue is often of suboptimal quality.

58. The use of xenogeneic material, on the other hand, may provide a possibility to optimise the procurement technique which may improve the quality of the cells. It might also serve to improve the ability of medical staff to prepare and plan xenotransplantation procedures while at the same time providing a larger accessibility to xenotransplant material. Furthermore, xenotransplantation avoids some of the ethical problems connected with the use of tissue from human aborted fetuses.

59. As in any other clinical procedure, patients should be selected amongst those for whom the likely benefits outweigh the potential risks. Considering the lifelong surveillance and lifestyle restrictions that may be necessary in xenotransplantation it is reasonable to reserve xenotransplantation for serious or life threatening disorders. Another prerequisite should be that safe and effective alternative treatments have not been developed or are not available to all the patients in need. The International Society for Heart and Lung Transplantation, at their April 2000 meeting in Osaka, Japan[28], made public a set of recommendations on patient selection criteria and experimental prerequisites to heart xenotransplantation. These can also serve as a basis for setting up requirements.

60. It should be noted that the consideration of a xenotransplantation procedure may evolve with time and that this should be taken into account in indent i. Indeed, some procedures may eventually be considered as safe, while others are set aside, with the accumulation of experience.

Indent ii.: Data suggesting suitable efficacy

61. The expression “clear therapeutic benefit” should be defined for the individual xenotransplantation proposed and the term should be interpreted to cover a number of benefits in different fields. However, the importance of these benefits should always be weighed against the risks for patients and for society.

First indent:

62. The precise technical requirements to demonstrate sufficient efficacy of the proposed xenotransplantation can only be addressed on a case by case basis. Precise requirements have not been laid down in individual countries. However, the Xenotransplantation Commission of the Spanish Committee of Transplants, in their 1998 recommendation[29], has proposed the following "indispensable requirement" in terms of pre-clinical efficacy: *"Survival and adequate function of the cells, tissues or organs grafted during a period of at least 6 months."* This statement can serve as a broad basis for further elaboration because it indicates that a sufficient pre-clinical period for demonstrating efficacy should be required. However, the following should also be taken into account:

- the nature of the xenotransplant (e.g. whole organ such as heart, isolated cells such as dopaminergic neurons, tissues such as pancreatic islets, …);
- the performance level of the xenotransplant required to reach the expected benefit (stage of differentiation or growth, metabolic functions, secretions, ability to proliferate, physiological regulations,…);
- the medical condition of the potential human recipients;
- the prognosis of the condition to be treated in the absence of a xenotransplantation (i.e. with conventional treatments);
- the source animal species;
- the recipient animal species and its relevance to the prospective xenotransplantation;
- the data pertaining to the quality of life of the recipient animals and their relevance to the xenotransplantation (e.g. level of immune suppression, side effects of the concomitant treatments, global physiology of the recipient,…).

63. The use of animal models is important in demonstrating adequate function of a xenotransplant, and it is recognised that the use of non-human primates is likely to be necessary at some stage in the

[28] International Society for Heart and Lung Transplantation: Twentieth Annual Meeting and Scientific Sessions. Osaka, April 5-8, 2000.

[29] Spanish Xenotransplantation Commission: Recommendations for the regulation of xenotransplantation activities in Spain, 1998.

development programme before the procedures are approved for use in humans. However it is expected, in accordance with the provisions of Convention ETS 123 of the Council of Europe and Directive 86/609/EEC of the European Union that animals will only be used where there is no alternative, and that non-human primates in particular will only be used where no other suitable species is appropriate. In general, progression to non-human primate studies should only follow a thorough and critical assessment of the need to use these species, including a detailed evaluation of in-vitro development work and, where appropriate, development work in other animal models. Every effort should be made to limit the duplication of research on any species, and to refine the use of animals, for example by improved husbandry and care practices. The programme should be subject to continuous review to ensure that animal use and suffering is minimised. In this context, it is generally accepted that non-human primates should not be used as source animals, both because of cross-species infection risks and because of the serious welfare implications of keeping these animals in biosecure facilities (see Article 11). However, it is recognised that the use of non-human primates as models is necessary to the pre-clinical evaluation of the efficacy of xenotransplantation, especially in terms of whole organ transplantation. The pre-clinical use of animals as recipients, and particularly non-human primates, is another factor to take into consideration when defining the period of time required for demonstrating safety and efficacy. This period should be sufficient to allow both demonstrative and convincing assessment but also calculated to minimise, as far as possible, the suffering caused to the animals.

64. The American Society for Testing and Materials issued draft guidelines for discussion[30] in which the pre-clinical requirements for tissue and cell products, whether allogeneic or xenogeneic, are outlined. The three classical aspects of therapeutic products, i.e. quality, safety and efficacy, are considered. These can also serve as a basis for further elaboration.

Second indent:

65. A transplant from a distant species, such as a pig, to a human person elicits a very strong response, termed hyper-acute rejection whereby the organ turns into a black, swollen, useless mass, within several minutes or hours. Moreover other rejections exist such as acute vascular and cellular rejections which may occur within days of transplantation and chronic rejection which may suddenly appear months or even years after the operation. This provision states, therefore, that pre-clinical studies should provide sufficient reasons to believe that the problems related to rejection can be overcome.

Indent iii.: Risks related to xenotransplantation

66. In any medical procedure such as xenotransplantation, the risks to the patient should be properly evaluated and should be balanced against the potential therapeutic benefits which may result (principle of proportionality).

67. Moreover, xenotransplantation should only take place if it is expected to provide better results than other therapies available to the patient. In this context, better results should be interpreted to cover several possibilities, for example, xenotransplants cannot be expected to provide better results than the survival rates currently obtained with human allotransplants.

Infectious risks of xenotransplantation

68. Xenotransplantation creates particular conditions where transmission of known or unknown pathogens from source animal to human recipient becomes a possibility and might ultimately become a public health risk. A number of factors contribute to this situation since:

- the transplantation bypasses the recipient’s normal physical protective barriers;
- the recipient, in many cases, will be in an immuno-compromised state in order to promote xenotransplant acceptance;
- the recipient will be continuously exposed to a xenotransplant in which pathogens may be present, thereby increasing the risks of the micro-organisms adapting to the human species;
- clinical recognition of a previously unknown, possibly slow-developing, disease may be difficult;
- laboratory tests may be inadequate or lacking altogether.

[30] Living Cells Task Group, Committee F04, American Society for Testing and Materials (ASTM). Draft Standard: Standard Guide for the Development of Tissue-Engineered Medical Products with Living Cells, 1999.

Need for experimental data to evaluate the risk of xenosis

69. Even under the most stringent conditions, a number of potential pathogens, in particular certain viruses, cannot be eliminated. Of particular concern are (a) retroviruses, especially endogenous retroviruses, which constitute part of the genome of the source animals, and (b) prion diseases. Therefore, because infectious risks cannot, at present, be completely eliminated through animal breeding techniques, the screening of source animals and the xenotransplant procurement procedures, it is necessary that the planned xenotransplantation should have been thoroughly tested experimentally. Thus, tests studying the potential for xenotransplantation to cause infectious diseases in the recipients should be performed during a sufficiently long period of time without any evidence of an increased risk being observed. In this respect, any research involving animals should fully address the relevant ethical and animal welfare concerns and comply with relevant regulations (such as Convention ETS 123). These issues are further addressed in Chapter V of the Recommendation relating to the protection of animals.

70. In the event of any transmissions of an infectious agent arising, an appropriate monitoring period should be required to evaluate the consequences. As an example, the Spanish Xenotransplantation Commission, in their 1998 Recommendation[31], have proposed the following three "indispensable requirements" to demonstrate pre-clinical safety:

- Demonstrated an absence of transmission of infectious agents in the recipient animal during a period of at least 6 months;
- Demonstrated an absence of any non-accidental transmission of infectious agents to the caretakers and other personnel involved in the research programme;
- Demonstrated, in the case of transmission of any infectious agents, that a minimum follow-up of one year has been carried out to evaluate the consequences both to the recipient and to the other animals in contact with the source animal.

71. However, the limited number of pre-clinical testing studies that good research practice recommends when using animals, and particularly non-human primates, entails that the lack of transmission of infectious diseases from the source animal to the recipient will not rule out completely a risk of xenosis. Thus, the consequences for the recipient of known infectious agents present in the source animal which cannot be excluded by the pathogen-free qualification should be explicitly investigated.

Non-infectious risks

72. Non-infectious risks should be explored in the pre-clinical xenotransplantation investigations. The details should be addressed on a case by case basis. Appropriate data should be provided to assess in particular:

- the risks linked to the immunological manipulation of the recipient and/or of the xenotransplant;
- the risks linked to the physiological adaptation of the xenotransplant to its new environment;
- the potential psychological or sociological risks to the recipient and/or his or her close personal contacts.

Article 13 – Information to be given to patients

73. Information given to the patient is an essential element for the validity of his or her consent. Paragraph 1 of this Article enunciates the general content of the information to be provided. Paragraph 2 addresses issues specific to information on xenotransplantation procedures.

Paragraph 1

74. Patients participating in a xenotransplantation should be adequately informed in a comprehensible manner of the nature, objectives, possible benefits, potential risks and consequences of the procedure, as well as of any constraints that may be linked to it.

75. It is important to ensure that patients are given all the appropriate information, which should be presented in an unbiased manner and in a way that should easily be understood by lay people. During the

[31] Spanish Xenotransplantation Commission: Recommendations for the regulation of xenotransplantation activities in Spain, 1998.

decision-making process, the patient should have access to discussions both with independent experts not involved in the proposed xenotransplantation and members of the team.

Paragraph 2

76. The patient should be informed of the constraints associated with the specific xenotransplantation procedure that he or she is planning to undergo.

77. This paragraph lists the most relevant personal constraints, which may directly affect the patient. The constraints will vary, in conformity with the principles of necessity and proportionality, depending on the nature and the circumstances of the procedure. If a specific xenotransplantation procedure has already been used as a clinical treatment for a sufficiently long period of time and if there is sufficient evidence to show that this procedure is safe, the constraints would be proportional to the risks perceived. This would happen, for example, for burns patients using human skin cells grown on animal feeder cells. If, on the other hand, a specific xenotransplantation procedure remains an experimental activity or is in clinical practice but continues to be perceived as being associated with high risks, then the patient should be informed of the more stringent constraints associated with the procedure.

78. Paragraph 2*b*. addresses the requirement for the patient to provide information to the medical team concerning his or her current close personal contacts so that, where there is a need to do so, they may also be made aware of the risks of infection and the constraints associated to xenotransplantation. If the patient does not agree to his or her close personal contacts being informed when it is considered there is a need to do so then the xenotransplantation should not take place.

79. Because of the potential risks of infection and the possible constraints resulting from these risks, paragraph 2*g.* specifies that the patient should, where necessary also be notified, and agree, that a medical team should provide future close personal contacts with information which may help them respond to xenotransplantation concerns. Thus, it would be the recipient's responsibility to put future close personal contacts in relationship with an appropriate medical team having experience in xenotransplantation so that they may be given this information. The requirement for patients to agree that appropriate information is provided to future close personal contacts is important since the xenotransplantation team may not be aware of the existence of these contacts (see Article 14).

80. Documented informed consent and recipient education should include, in addition to the constraints presented in Article 13 paragraph 2, information on the following:

- the known and unknown potential for infection by zoonotic agents and the unknown risk of transmission of xenogeneic infectious agents to the recipient's close personal contacts;
- the need for isolation procedures during hospitalisation and their nature;
- the possibility of future isolation which may become necessary in the event of a contagious or previously unknown illness occurring;
- the fact that immunosuppressed persons may be at an increased risk of xenogeneic infection and that specialised precautions (e.g. dietary, personal, travel) may be required following hospital discharge;
- the need for the patient to comply with long-term (potentially lifelong) surveillance necessitating routine physical evaluations with archiving of tissue and/or serum specimens including the schedule for clinical and laboratory monitoring;
- the need for any serious or unexplained illness arising in the recipient or his or her close personal contacts to be reported to a physician without delay;
- the unknown impact of possible psychological or social problems for xenotransplant recipients, their close personal contacts or other individuals in society;
- the possibility that in the event of death, the need for a complete autopsy may exist;
- the requirement that recipients should never donate blood, or any blood constituent or any other body fluid, tissue or part for use in humans.

Paragraph 3

81. The special constraints which may be connected with xenotransplantation should be explained repeatedly and in detail since they may conflict with a number of national and international human rights regulations. This is explained in the discussions with the representatives of the European Court of Human Rights (see Appendix) which states that "[m]any of the rights in the Convention [on Human Rights] were subject to permissible restrictions and involved establishing a proper balance between competing interests."

It should also be noted that restrictive measures such as quarantine procedures are not specific to xenotransplantation but are also applied for other contagious illnesses when they occur. The possibility for the state to intervene and take coercive measures should be discussed and assessed with respect to the national legal situation.

Article 14 – Information to be given to close personal contacts of the patient

82. In contrast to most other therapeutic procedures, xenotransplantation has direct consequences on the lifestyle of the patient's close personal contacts. Thus, in accordance with Article 16, paragraph 1, indent ii., the patient should be aware that he or she should, where required, provide to the medical team the necessary information concerning his or her current close contacts. Furthermore the patient should accept that his or her current and future close personal contacts may need to be informed of the envisaged xenotransplantation and of the risks and constraints possibly associated with such a procedure. This is especially important with respect to the measures to be taken to minimise potential infections (Spain[32], Canada[33], United Kingdom[34], United States[35]).

83. However, this information should only be provided by the medical team to the close personal contacts if the patient has given his or her informed consent to such a course of action; if the patient refuses to authorise the provision of such information, the xenotransplantation should not be carried out (see comments on Article 16, paragraph 1, indent ii.).

84. In this Article close personal contacts can be described as persons who have "engaged in activities that could result in intimate exchange of body fluids"[36]. For example, close personal contacts could include:

- persons with whom the recipient is having sexual contact without protection,
- persons with whom the recipient is exchanging blood or saliva,
- children which are breast-feeding from a xenotransplant recipient,
- "household members who share razors or toothbrushes"[36], and
- "health care workers or laboratory personnel with repeated percutaneous, mucosal or other direct exposures."[36]

85. At the same time, the FDA draft guidance document entitled "Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts"[36] indicates that the "[s]haring of housing or casual contact, such as hugging or kissing without the exchange of saliva, would not be interpreted as intimate contact."

86. It is also desirable that the recipient and close personal contacts should never donate body fluids or body parts for use in humans following a xenotransplantation. Such a requirement is explicit in the United States and Canadian documents[37,38].

87. If a close personal contact refuses to listen or abide to the information given by the medical team, then the medical team should consider whether the xenotransplantation should take place on a case by case basis. It should be noted, however, that with respect to xenotransplantation research, a specific right to participate in such a procedure does not exist.

88. If the close personal contact and the patient begin a relationship after the xenotransplantation, it is the patient's responsibility to provide information to be given to the close personal contact or to ensure that this information is otherwise provided. For example, the patient should inform any future close personal contacts of the possibility of obtaining additional information from a medical team.

---

[32] Spanish Xenotransplantation Commission: Recommendations for the regulation of xenotransplantation activities in Spain, 1998.

[33] Blood, Tissues, Organs and Xenografts Project, Policy Division, Therapeutic Products Programme, Health Protection Branch, Health Canada: Proposed Canadian Standard for Xenotransplantation, Draft 14, July 1999.

[34] Draft Report of the Infection Surveillance Steering Group: Future guidance on infection surveillance aspects of xenotransplantation (www.doh.gov.uk/ukxira/index)

[35] Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). *Federal register* 1996; 61(185): 49919-32.

[36] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (CBER): FDA Draft Guidance document entitled "Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and their Intimate Contacts", February 2002.

[37] Blood, Tissues, Organs and Xenografts Project, Policy Division, Therapeutic Products Programme, Health Protection Branch, Health Canada: Proposed Canadian Standard for Xenotransplantation, Draft 14, July 1999.

[38] Draft Public Health Service Guideline on Infectious Diseases Issues in Xenotransplantation (August 1996). *Federal register* 1996; 61(185): 49919-32.

Article 15 – Information to be given to the professional staff involved in xenotransplantation

89. Because professional staff involved in xenotransplantation may also be exposed to infectious agents, it should be ensured that these professionals are fully aware of the potential risks and consequences related to such a procedure including possible constraints associated with their involvement in the procedure.

Article 16 – Consent to xenotransplantation

Paragraph 1

Indent i.

90. No person should undergo xenotransplantation without his or her free and informed consent. A patient's consent is considered to be free and informed if it is given on the basis of objective information as to the nature and the potential consequences (including any necessary specific constraints) of the xenotransplantation and its alternatives, in the absence of any pressure from anyone. Information on the risks involved in the xenotransplantation and in alternative courses of action should cover not only the risks inherent in xenotransplantation but also any risks related to the individual characteristics of each patient, such as age or the existence of other pathologies.

91. Often, the decision to consent to a procedure will influence the lifestyle of the patient and his or her close personal contacts including the requirement for lifelong surveillance and the possibility of extensive coercive measures. The legal basis for the performance of lifelong surveillance of patients will probably differ between countries but, in most cases, a strong suspicion or a definite demonstration of a potential risk is likely to be necessary.

92. Information relevant to consent should be presented and explained to the patient or, if the patient does not have the capacity to consent, the next-of-kin (or person(s) responsible) by an independent person, such as a patient advocate (helped, if necessary, by an interpreter) who is not a member of the xenotransplantation team. The patient or the next-of-kin (or person(s) responsible) should have enough time to consider the information and always more than 24 hours before the proposed xenotransplantation.

Indent ii.

93. Xenotransplantation should not be carried out without the provision by the patient to the medical team of the necessary information concerning his or her current close personal contacts. The patient should also accept that his or her current and future close personal contacts may need to be given the information mentioned in Article 14 by the relevant medical team so that they may also become aware of the risks of infection and the constraints associated to xenotransplantation.

Paragraph 2

94. Freedom of consent implies that consent may be withdrawn at any time prior to a xenotransplantation and that the decision of the person shall be respected once he or she has been fully informed of the consequences. However, this principle does not mean, for example, that the withdrawal of a patient's consent once he or she has been exposed to the animal material should always represent an end to the possible constraints mentioned in Article 13. Because of the risks of infection, a state may indeed impose constraints to protect public health.

Article 17 – Counselling and support

95. Xenotransplantation is a very complex process involving not only medical but also ethical, psychological and social aspects. Because of this, the patients and their close personal contacts should be given proper information and have access to counselling and support that is individually adapted to the patients' and their close personal contacts' backgrounds and previous experiences. It is also important that patients and their close personal contacts be given appropriate updates on developments in xenotransplantation and have long-term access to counselling in addition to education about xenotransplantation and its consequences.

Article 18 – Right to medical care

96. The decision whether or not to participate in a xenotransplantation should be taken without any fear that a refusal to participate in the procedure would jeopardise the possibility of obtaining good medical care or lead to impaired relations with the medical team in the future. This is a prerequisite when approaching patients for participation in any clinical procedure including xenotransplantation. Even if it may seem obvious to the clinician or investigator, it is important that this is made clear to the patients and their close personal contacts so that inappropriate pressure during the decision making process is avoided.

97. Though xenotransplantation can be used for some patients instead of allotransplantation, a refusal to participate or a withdrawal from a xenotransplantation should not prejudice a patient's right to benefit from an allotransplant if medically indicated. Similarly, if a suitable human transplant becomes available after a patient has consented to participate in a xenotransplantation, the patient should still be considered for an allotransplantation. If a patient has been removed from the allotransplant waiting list because of a xenotransplantation which eventually proves unsuccessful, the patient should be put back on the waiting list without the xenotransplantation having influenced the patient's position on the list. A patient could of course still be given priority, with respect to an allotransplant, for medical reasons.

Article 19 – Patients not able to consent

Paragraph 1: Xenotransplantation other than in clinical research

98. Xenotransplantation other than in clinical research for patients not able to consent should only be allowed if there is no therapeutic alternative of comparable effectiveness available to the patient. Moreover, for patients unable to consent, xenotransplantation should only be authorised if there is adequate evidence, in accordance with internationally accepted scientific standards, that no risks, in particular of infection to the general population, exist and the therapeutic benefit of the xenotransplantation has been established as indicated in Article 5, paragraph 2.

99. Because of the specific vulnerability of patients unable to consent this Article also specifies that they may only be included in a xenotransplantation other than in clinical research if the intervention is expected to result in a direct and important benefit for the patient which would offset the constraints and conditions to which the person will or may be subjected according to Articles 13 and 14. Furthermore, the representative or an authority or a person or body provided for by law, after receiving the information referred to in Article 13, should have authorised both the intervention and the provision of the necessary information to the present and future close personal contacts of the patient.

Paragraph 2: Clinical xenotransplantation research

100. As a principle, a patient incapable of giving informed consent should not undergo clinical xenotransplantation research. Only under exceptional circumstances, and when there is adequate indication, on the basis of prior clinical research, that the clinical xenotransplantation research procedure might be lifesaving and there is no alternative means of saving the life of the particular patient unable to consent, should it be considered. Under all circumstances, the intention to include patients incapable of giving informed consent should be clearly stated in the application to the xenotransplantation body defined in Article 5 and should be specifically considered during the authorisation procedure.

101. Because of the specific vulnerability of patients unable to consent this Article also specifies that they may only be included in clinical xenotransplantation research if the intervention is expected to result in a direct and important benefit for the patient which would offset the constraints and conditions to which the person will or may be subjected according to Articles 13 and 14. Furthermore, the representative or an authority or a person or body provided for by law, after receiving the information to be given to the patient referred to in Article 13, should have authorised both the patient's participation in the clinical xenotransplantation research and the provision of the necessary information to the present and future close personal contacts of the patient.

102. Though it is important that patients unable to consent should be protected against undue experimentation, it has also been pointed out that such patients should have a right to be involved in

research related to problems that cannot be studied in other groups. These patients would, otherwise, be excluded from the development of new treatment strategies.

Article 20 – Confidentiality

103. Personal data concerning the recipients and their close personal contacts should be treated as confidential and handled in accordance with the rules on personal data protection. Here, the principles laid down in the *Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data* of 28 January 1981 (ETS No.108) should be observed. In particular, Article 5.b of this Convention provides that personal data are *"stored for specified and legitimate purposes and not used in a way incompatible with those purposes"*. Parties should take account of other national or international instruments, such as Recommendation R (97)5 of the Committee of Ministers to member states on the protection of medical data and, where applicable, Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on free movement of such data.

104. In xenotransplantation, it is nevertheless essential that the principle of confidentiality should not prevent the medical team involved in any procedure from obtaining the necessary information on the recipient and their close personal contacts, subject to appropriate safeguards to ensure adequate data protection.

Article 21 – Compulsory constraints

105. An infectious event related to a xenotransplantation is a complication that not only affects the patient but may also pose a risk to close personal contacts, professional staff involved in xenotransplantation and even to the general public. Because of this, and when a xenotransplantation has already been carried out, a state may intervene, in accordance with national law and the principles of necessity and proportionality, if the patients or their close personal contacts refuse to comply with the agreed surveillance, lifestyle restrictions or treatment schedules. It is important that patients and their close personal contacts are fully informed of the nature of such an intervention. States should also have regulations in place relating to xenotransplantation which take into account the risks of infectious disease as stated in the provisions of the Explanatory Report relating to Article 4.

106. Patient compliance with surveillance and lifestyle restrictions will greatly influence the risk for the public if transmission of a microbiological agent occurred. It is thus very important that patients involved in xenotransplantation are likely to be compliant with the xenotransplantation regulations. Non-compliance with immunosuppressive medication and the postoperative follow-up is today one of the most common causes for renal graft loss in many countries. Special care should be taken in this respect and psychological evaluations should be included in the selection process.

Chapter V – Protection of animals

Article 22 – Compliance with animal protection regulations

107. A source animal is an animal that will provide cells, tissues or organs for use in xenotransplantation. The animals used to provide eggs or sperm in the breeding programme to produce source animals are generally referred to as dams or sires respectively.

108. Source animals for xenotransplantation will be reared under highly specialised conditions comparable to those for laboratory animals. They are likely to be derived using techniques designed to improve and maintain their microbiological status which give rise to associated welfare concerns. Source animals should also have to undergo scientific procedures (e.g. blood and tissue typing) to ensure their suitability for subsequent use. Additionally, the animals are likely to need to undergo regular, detailed monitoring, not only with respect to their welfare but also to assess and ensure their suitability for use. Since all of the techniques applied to the animals are being performed for a scientific purpose Directive

86/609/EEC[39] and Convention ETS No. 123[40] should apply to the source animals as well as to those used for research purposes.

109. Pigs have been considered to be the preferred source animal for xenotransplantation and most of the detailed guidelines available for source animal husbandry and care refer to this species. However, the widening of the definition of xenotransplantation means that other species may now be used. The detailed points in the explanatory notes refer to pigs but the principles should apply to all species used.

110. Detailed guidance on the maintenance of pigs in xenotransplantation programmes has been developed in documents such as the UK Home Office's *Draft Code of Practice for the Housing and Care of Pigs used as Xenotransplant Source Animals*[41]. These documents set out standards for all xenotransplantation programmes. Further guidance regarding the maintenance and welfare of pigs is available in the Report of the EU Scientific Veterinary Committee, 1997[42] and in the scientific literature[43, 44].

111. It should be noted that this Article indicates that the "principles" of Appendix A of the *European Convention for the protection of vertebrate animals used for experimental and other scientific purposes* should be complied with. Indeed, although this European Convention foresees that there are exceptions, it may not always be possible to fully follow the provisions of this Appendix because of the requirements of biosecurity necessary for xenotransplantation.

Article 23 – Husbandry, care, use and requirements of animals

112. Pigs are sentient, intelligent and inquisitive animals that have retained many of the complex behavioural characteristics of their wild ancestors. These include rooting and exploratory behaviour, and social interactions within small, stable groups. They have limited thermo-regulatory ability, but their hearing and, in particular, their olfactory abilities are highly developed. Housing, husbandry and general management of pigs should take account of these needs.

113. The optimal environment depends on many factors including age, feeding regime and social circumstances. There are general guidelines in the scientific and technical literature[45, 46, 47, 48, 49] but decisions regarding the adequacy of the environment on a day to day basis should be based on frequent observation by an experienced stockperson of the behaviour and physical well being of the pigs themselves.

---

[39] European Union, 1986 Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of Member States regarding the protection of animals used for experimental and other scientific purposes.

[40] Council of Europe, 1986, European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes.

[41] Home Office Draft Code of Practice for the Housing and Care of Pigs used as Xenotransplant Source Animals. UK Home Office, HMSO, 2000.

[42] The Welfare of Intensively Kept Pigs – Report of the Scientific Veterinary Committee. Adopted 30th September 1997. Doc XXIV/B3/ScVC/0005/1997 final.

[43] Lean, I. (1999) Pigs. In R. Ewbank, F. Kim-Madslien & C. B. Hart (eds) Management and Welfare of Farm Animals: the UFAW Farm Handbook. UFAW, Wheathampstead. pp 137-166.

[44] Holtz, W & Bollen, P (1999) Pigs and minipigs. In T. B. Poole (ed) The UFAW Handbook on Care and Management of Laboratory Animals. Seventh Edition. Volume 1, pp 464-488.

[45] The Welfare of Intensively Kept Pigs – Report of the Scientific Veterinary Committee. Adopted 30th September 1997. Doc XXIV/B3/ScVC/0005/1997 final.

[46] Lean, I. (1999) Pigs. In R. Ewbank, F. Kim-Madslien & C. B. Hart (eds) Management and Welfare of Farm Animals: the UFAW Farm Handbook. UFAW, Wheathampstead. pp 137-166.

[47] Holtz, W & Bollen, P (1999) Pigs and minipigs. In T. B. Poole (ed) The UFAW Handbook on Care and Management of Laboratory Animals. Seventh Edition. Volume 1, pp 464-488.

[48] Bruce J.M. & Clark J.J. (1979) Models of heat production and critical temperatures for growing pigs. Animal Production, 28, 353-369.

[49] RSPCA Welfare Standards for pigs ISBN 1 898331 448 RSPCA June 2000.

114. Animals should be housed in facilities appropriate for the species, built and operated in line with recommendations available such as the *Guide for the Care and Use of Laboratory Animals*[50] and meet regular inspection requirements, including details of source animal and health surveillance record systems.

115. To achieve satisfactory standards of welfare for pigs, the systems of accommodation, husbandry and care should ensure that the animals have:

a) company of their own kind, allowing them to live in stable groups with other familiar individuals - animals should never be held in complete isolation without visual, auditory and olfactory contact with other pigs.

b) adequate amounts of space, in both a lying area (in which all pigs should be able to lie down together in lateral recumbency) and the general 'loafing'/dunging area, in order to allow all pigs to move around freely and be able to escape and hide from other pigs if necessary.

c) housing which protects against physical discomfort, providing a clean, dry, comfortable lying area, suitable non-abrasive, non-slip flooring, and an enclosure without sharp protrusions or other characteristics likely to cause injury.

d) adequate quantities of clean, fresh water continuously available; adequate quantities of diet formulated to satisfy the nutritional requirements of the animals and ensure good welfare. Where animals are held in groups, care should be taken to ensure that subordinate animals have adequate access to food and water to avoid potential sources of aggression.

e) a thermally comfortable environment, ensuring that the temperature remains within the pigs' thermoneutral range[51] and avoiding lengthy exposure to low humidity.

f) an acceptable atmosphere, maintaining appropriate ventilation for the stocking densities in use; ensuring that aerial contaminants (e.g. ammonia, inhalable dust) are kept within non-aversive and non-harmful limits; and avoiding draughts.

g) appropriate lighting for a period equivalent to normal daylight hours, and providing a period of darkness - pigs should never be kept in continuous complete darkness.

h) minimum levels of continuous background noise and avoidance of unexpected loud noise since high levels of noise are potential stressors.

i) environmental enrichment, providing adequate amounts of straw or other suitable materials for manipulation, to satisfy pigs' behavioural needs in terms of rooting, recreational and investigative behaviour.

j) competent, knowledgeable stock-persons who understand the pigs' needs and behaviours, and are dedicated to promoting their well-being and preventing or minimising any fear, distress and discomfort at all times - gentle, calm human contact with the pigs is important, as this will minimise stress during handling and procedures.

k) competent, knowledgeable, veterinary care, by those with specialist experience and understanding of pig health and welfare.

Space allowances

116. Minimum pen dimensions and space allowances for individual and groups of animals are specified below. These comply with the current recommendations in the European Convention ETS No. 123[52] and

[50] Guide for the Care and Use of Laboratory Animals, NIH publication no 86-23, revised 1985.

[51] Bruce J.M. & Clark J.J. (1979) Models of heat production and critical temperatures for growing pigs. Animal Production, 28, 353-369.

[52] Council of Europe, 1986, European Convention for the Protection of Vertebrate Animals used for experimental and other scientific purposes.

Directive 86/609 EEC[53]. Note that the shape of the pen, its complexity and contents are as important to the animal as overall size.

[53] European Union, 1986 Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of Member States regarding the protection of animals used for experimental and other scientific purposes.

Space Allowances for Weaners, Growing & Adult Pigs:

Species - Pigs	Minimum Floor Area – Groups (per pig)	Minimum Floor Area - Single Pigs	Minimum Feed Rack
Up to 10 kg	0.25m²	1.0m²	0.15m
10 – 20 kg	0.5m²	1.5m²	0.20m
20 – 30 kg	1.0m²	2.0m²	0.20m
30 – 50 kg	1.3m²	2.0m²	0.25m
50 – 100 kg	2.0m²	3.0m²	0.30m
100 – 150 kg	2.7m²	4.0m²	0.35m
Over 150 kg	3.75m²	5.0m²	0.40m
Adult Boars	-	7.5m²	0.50m

Service pens should have a minimum floor area of 10.5m², to allow a sufficient area for mating.

Breeding animals

Sows

117. The design of the farrowing area should be appropriate for the size of the sow, to allow the animal to lie down comfortably, to stand upright and to expose all teats to the piglets. The sow should be provided with a solid floored lying area, at least equal to 75% of the overall area and some form of nesting material should be provided, especially as farrowing approaches.

118. The accommodation where sows and piglets are kept should enable the fulfilment of the special behaviour patterns of the sow before and after parturition, and those of the piglets after birth. Thus even though the use of farrowing crates can safeguard piglets' survival and welfare under some conditions, the close confinement of sows during the perinatal and suckling periods should be limited as far as possible and loose housing systems should be preferred. Farrowing crates significantly limit the behavioural repertoire of the sow and therefore the sow should be given greater freedom in later lactation when piglet viability is well established. From five days after farrowing, sows should have at least enough space to turn around easily and the more welfare friendly systems which allow this should be promptly adopted.

119. The period of confinement should be minimised, with animals crated no more than 5 days pre-farrowing, and returned to an extensive group housing system at weaning, generally by 4 weeks post-partum, or earlier if early weaning practices (segregated/medicated early weaning) are considered necessary and are used.

Boars

120. Adult boars are commonly housed singly. However, animals raised together from an early age have been maintained successfully in pairs as adults. Group housing is therefore encouraged, provided that social harmony can be maintained. If single housing is unavoidable then auditory and olfactory stimuli with other pigs should be available at all times, with the opportunity for visual and safe tactile contacts.

121. Boars tend to be physically segregated for long periods; therefore particular care should be taken to provide an enriched environment that addresses their behavioural needs.

Additional animal requirements

122. Young animals should be weaned into social groups. Siblings from one litter should not be separated unnecessarily.

123. Some types of biocontainment facilities are totally inappropriate for some species. For example, pigs should not be wholly reared in gnotobiotic conditions and should not be reared beyond the age of four weeks in an isolator.

124. Pigs living within a barriered animal unit are totally dependent on humans for their health and well being. The physical and psychological state of the animals will be influenced by their surroundings, food, water and the nature and quality of the care and attention provided by the animal house staff.

125. Restricted environments can lead to behavioural and physiological abnormalities. Adequate complexity is required within the basic pen design to allow the animal to carry out a range of normal behaviours. For example, visual barriers can be useful to allow the pigs to control social interactions and provide refuges. In extensive systems, pigs spend many hours exploring their environment, using their highly sensitive snout to root; laboratory housed pigs have little opportunity to express this sort of behaviour. In the absence of suitable foraging substrate and when there is insufficient diet to maintain satiety, abnormal stereotypic behaviours, such as bar chewing, and increased aggression can develop. Material, such as straw, can provide for many of these behavioural requirements, and should be provided where possible. If such material cannot be provided because of the nature of the barrier system, then alternative enrichment strategies should be included e.g. food balls; other 'toys'; pebble trays; chains; scratching posts; showers.

126. Where pigs develop stereotypes or abnormal behaviours that injure other animals (e.g. tail, ear or vulva biting) additional enrichment to encourage foraging/rooting should be provided as a matter of urgency and an appropriate enrichment programme developed and implemented. If necessary, animals may need to be removed from the group.

127. Castration, tooth clipping or grinding, and tail docking should not be necessary for pigs produced for xenotransplantation programmes[54]. They should only be carried out to deal with specific welfare problems by specially trained and competent persons using appropriate equipment. If these do arise then the cause should be examined and if resulting from the husbandry system this should be adjusted to avoid repetition.

Training of Staff

128. Appropriate training of staff is essential to ensure that high standards of pig husbandry and care are provided, and that barrier security can be maintained. The importance of such training was recognised by the Multilateral Consultation of Parties to Convention ETS No.123[55]. Attendance on a course satisfying the requirements of the appropriate Federation of European Animal Science Associations (FELASA) training category should be strongly recommended.

129. Training should include an introduction to the natural history and behaviour of the pig, which will illustrate their needs in a captive breeding system. Animal care staff should be trained to recognise normal behaviour, in order that any abnormalities can be identified at an early stage. Pig husbandry, care and welfare, principles of barrier production and maintenance, barrier hygiene, internal management practices, breeding and health record keeping practices should also be included.

Article 24 – Responsibility for husbandry and care of animals

130. Records should be kept of the numbers of animals used in both xenotransplantation and pre-clinical procedures.

Article 25 – Surgical derivation and early weaning techniques

131. Records should be kept of all surgical derivation and segregated/medicated early weaning procedures and any associated welfare problems. Such records should be subject to regular review.

Article 26 – Transport of animals

132. All transport should be carried out in strict compliance with EU and other international legislation (the *European Convention for the Protection of Animals During International Transport*[56] (revised)*;* Draft *Code of Conduct for the International Transport by Road of cattle, sheep, goats, pigs, horses, poultry, deer, reindeer,*

[54] The National Committee for Pig Breeding, Health and Production, Copenhagen, Denmark. Report No. 286. Tooth grinding compared with clipping of teeth in newborn piglets. Nielson, N.P.

[55] Multilateral Consultation of Parties to Convention ETS – No. 123 (see resolution on education and training of persons working with laboratory animals adopted by the Multilateral Consultation, 3 December 1993).

[56] The European Convention for the Protection of Animals During International Transport (revised).

rabbits and ostriches[57]*)*. Detailed guidance specifically on transport of pigs is provided in the Draft Code of Practice published by the UK Home Office[58].

133. Only animals in good health should be transported. The time in transit should be kept to a minimum. Stress should be minimised by making animals as comfortable as possible in their pens or containers with due regard to conditions likely to prevail throughout the journey. Animals that are incompatible should not be transported together.

134. There is evidence that pigs may become travel sick[59] so withdrawal of food for four hours prior to transportation is recommended, although free access to water (and milk in the case of pre-weaned piglets) should be provided at all times. It should be noted, moreover, that since pigs should not be denied food for long periods, journeys should not be prolonged.

135. Pregnant animals should not be transported during the first six weeks of pregnancy, and particularly not within the last 11 days of the expected birth and the 48 hours thereafter (see the *European Convention for the Protection of Animals During International Transport* (revised)[60]). Special consideration should be given to the welfare of young piglets during transport, in particular with regard to the maintenance of suitable environmental controls and arrangements for feeding and watering.

136. Emergency plans should be in place to deal with possible problems during transport, such as vehicle breakdown.

137. Those in charge of pigs during transport should be trained with the necessary skills. Moreover they should be knowledgeable of the behaviour and physical needs of pigs. Drivers should be trained in such a way as to minimise risk of injury or stress to the animals.

Article 27 – Organ and tissue procurement from animals

138. Where surgery is to be performed, suitable operating facilities should be provided, including separate preparation areas for the animals, equipment and staff. General veterinary treatment rooms should also be provided.

139. Surgery and killing of animals should not be performed in rooms where animals are normally housed, unless in the case of the emergency killing of a badly injured animal, welfare may be further compromised by moving the animal.

140. To avoid animal suffering, the sequential harvest of solid organs from individual animals in xenotransplantation should not be permitted unless this is performed under a single general anaesthetic from which the source animal does not recover consciousness.

141. The procurement of tissues and cells from individual animals during xenotransplantation research should be undertaken in conformity with Article 11 of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (ETS No. 123), which states:

1. At the end of the procedure it shall be decided whether the animal shall be kept alive or killed by a humane method. An animal shall not be kept alive if, even though it has been restored to normal health in all other respects, it is likely to remain in lasting pain or distress.

2. The decision referred to in paragraph 1 of this article shall be taken by a competent person, in particular a veterinarian, or the person who, in accordance with Article 13, is responsible for, or has performed, the procedure.

---

[57] Draft Code of Conduct for the International Transport by Road of cattle, sheep, goats, pigs, horses, poultry, deer, reindeer, rabbits and ostriches.

[58] Home Office Draft Code of Practice for the Housing and Care of Pigs used as Xenotransplant Source Animals. UK Home Office, HMSO, 2000.

[59] Warriss, P.D. (1998) The welfare of slaughter pigs during transport. Animal Welfare, 7, 365-381.

[60] The European Convention for the Protection of Animals During International Transport (revised).

3. Where, at the end of the procedure:

a. an animal is to be kept alive, it shall receive the care appropriate to its state of health, be placed under the supervision of a veterinarian or other competent person and kept under conditions conforming to the requirements of Article 5. The conditions laid down in this sub-paragraph may, however, be waived where, in the opinion of a veterinarian, the animal would not suffer as a consequence of such exemption;

b. an animal is not to be kept alive or cannot benefit from the provisions of Article 5 for its well-being, it shall be killed by a humane method as soon as possible.

4. No animal which has been used in a procedure entailing severe or enduring pain or suffering, irrespective of whether anaesthesia or analgesia was employed, shall be used in a further procedure unless it has returned to good health and well-being and either:

a. the further procedure is one in which the animal is subject throughout to general anaesthesia which is to be maintained until the animal is killed; or

b. the further procedure will involve minor interventions only.

Article 28 – Collection of animal records

142. Biological samples and records from the source animal should be systematically archived. Archived items should include all the source animal's necropsy reports together with stored serum and plasma, viable leukocytes and samples of xenotransplant cells and tissues in addition to other major organs (spleen, liver, kidney, heart, bone marrow, gut, central nervous system).

143. If genetically modified animals are used, recording of any unusual or unexpected traits such as abnormal phenotypes or behaviour is very important in order to monitor the effects of the genetic modification which may not become apparent until at least the second generation. If abnormal traits are detected then additional justification for the use of these animals for xenotransplantation may be required.

Article 29 – Pre-clinical research

144. Since the European Convention and the European Council Directive addressing the protection of animals used for experimental and other scientific purposes mentioned in Article 22 may not be applicable in some member states, and in order to protect animals used in pre-clinical research, Article 29 of the Recommendation extends the protection provided by Articles 22 - 28 to all animals used in pre-clinical research. This is in addition to providing husbandry and care appropriate to the needs of animals and ensuring that any experimental technique is carried out in a humane manner. This includes following current international laboratory animal science principles such as seeking replacements for animals, reducing the numbers used and the refinement of interventions.

Chapter VI – Provisions relating to the ethical, social and psychological acceptability of xenotransplantation

Article 30 – Public debate

145. Because of the novelty of xenotransplantation and the potential risks involved both for the individual and the community, public information is crucial. This is especially the case since clinical xenotransplantation research using tissues and cells is already underway and the results of such activities in addition to any further clinical work should be carefully and fully monitored and reported. This will help scientists, legislators and the general public understand both what is involved in xenotransplantation and the consequences and implications of such a procedure. Indeed the information will provide the necessary framework for the development and application of licensing, monitoring and the surveillance of future xenotransplantations.

146. It is vital that all results - both negative and positive should be accurately reported and fully accessible both to the general public and to those who carry responsibility for the regulation and control of xenotransplantation. Negative results and consequences carry considerable weight in any assessment of further work and development of xenotransplantation technology.

147. Assessing the public's reaction, concern, approval or disapproval of xenotransplantation will require careful presentation through the various media of all information about xenotransplantation research and raises questions about how public debate on such issues is conducted and public opinion assessed.

148. The fact that certain xenotransplantation activities begun before any public information was provided does not mean that it is pointless to provide such information.

Chapter VII – Co-operation between parties

Article 31 – International co-operation in medical research

149. This Article indicates that member states should take appropriate steps to facilitate the co-ordination of research in xenotransplantation. This is important in order to improve the efficacy and safety of xenotransplantation, to avoid unnecessary duplication and to minimise animal use and suffering.

150. It is important that commercial concerns relating to xenotransplantation are included at the very beginning of the international co-operation and collaboration process so that their views and suggestions can be included in the discussions.

Article 32 – International co-operation in public health

151. In order to ensure that member states communicate without delay to national public health authorities of member states and other concerned states of any events, in particular of infection, possibly related to a xenotransplantation, all relevant information should be centralised at a national level. It would be desirable that an international registry of xenotransplantation together with an international data communication procedure is established to ensure that timely measures are taken to protect public health.

152. International co-operation and collaboration should also encourage different countries engaged in xenotransplantation to prepare a uniform set of guidelines. This should be undertaken both because international conventions require that states do not put their neighbours at risk and because much benefit may be obtained in sharing the experience arising from national deliberations regarding medical safety, research and clinical work.

Chapter VIII – Compensation for undue damage

Article 33 – Compensation for undue damage

153. This Article applies to the xenotransplantation field the general principle already contained in the Convention on Human Rights and Biomedicine (ETS No. 164), that any person who has suffered undue damage resulting from an intervention is entitled to fair compensation. The Convention uses the expression "undue damage" because in medicine some damage, such as amputation, is inherent in the therapeutic intervention itself.

154. The due or undue nature of the damage will have to be determined in the light of the circumstances of each case. The cause of the damage might take the form of either an act or an omission. In order to give entitlement to compensation, the damage must result from the xenotransplantation.

155. Compensation conditions and procedures are prescribed by national law. In many cases, this establishes a system of individual liability based either on fault or on the notion of risk or strict liability. In other cases, the law may provide for a collective system of compensation irrespective of individual liability.

156. On the subject of fair compensation, reference can be made to Article 50 of the European Convention on Human Rights, which allows the Court to afford just satisfaction to the injured party.

Chapter IX – Reports on the implementation of the recommendation

Article 34 – Implementation of the recommendation

157. Because of the possible new developments in xenotransplantation, guidelines in the form of recommendations were considered as being more appropriate to regulate this field than a Convention, whose entry into force usually takes a number of years. Accordingly, the present guidelines are in the form of an official Recommendation from the Committee of Ministers of the Council of Europe to all member states; they are also communicated to the non-member states who have participated in the drafting of this document. The Secretary General of the Council of Europe can ask any member state to provide an explanation on the manner in which its internal law ensures the effective implementation of any of the provisions of this Recommendation, of any xenotransplantation activity and on any adverse event as referred to in Article 9.

Appendix

Summary of the discussions with the representatives of the European Court of Human Rights concerning legal issues relevant to xenotransplantation

The representatives of the European Court of Human Rights introduced the Convention for the Protection of Human Rights and Fundamental Freedoms of the Council of Europe by explaining that it should be understood as a legal instrument aimed at securing individual rights and as such it may be of limited relevance to policy issues in the field of bioethics. Many of the rights in the Convention were subject to permissible restrictions and involved establishing a proper balance between competing interests.

In determining whether a restriction or "interference" is in conformity with the requirements of the Convention, the Court examines whether it has a proper legal basis, and in particular whether the law is accessible and the effect of its application is foreseeable, and whether the interference can be regarded as justified in a democratic society in pursuit of one of the legitimate aims specified in the Convention. In the context of xenotransplantation, this implied the need for a clear legal basis for obtaining informed consent and for providing an adequate explanation of the related risks.

The Convention did make provision for the compulsory confinement of individuals but only in specific cases, an exhaustive list of which was given in the Convention. In addition, detention had to be both "lawful" and "in accordance with a procedure prescribed by law" and the Convention added a variety of safeguards against arbitrary deprivations of liberty. More specifically, the Convention in Article 5(1)(d) permitted the lawful detention of persons to limit the spreading of infectious diseases.

With regard to Article 8 of the Convention, which protects the right to respect for, *inter alia*, private and family life, it was explained that interferences could be justified provided they were necessary in a democratic society. Moreover, in certain circumstances it might be considered that an individual, by giving consent to a particular interference, had waived his or her rights.

The representatives of the European Court of Human Rights concluded that the Convention did not address any rights to a treatment of a patient, as such, but might be relevant to the question whether a state had the appropriate legal framework and procedures in place to resolve any possible conflicts between actors. Furthermore, with specific regards to xenotransplantation, very little jurisprudence of any relevance could be found in the case-law of the Convention during the last 40 years.