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**OPINION
ON
THE STATE OF THE ART CONCERNING XENOTRANSPLANTATION**

**Adopted by
The Scientific Committee on Medicinal Products and Medical Devices
On 1st. October 2001**

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Background

1. During 1999 the Scientific Committee on Medicinal Products and Medical Devices (SCMPMD) discussed a list of emerging issues of public health importance related to medical treatment and likely concern in the future. Xenotransplantation, which involves the use of animal tissues in medical treatment, was one of these which carried a high priority and a working group was therefore established to scope the issue.

Purpose

2. The purpose of this opinion is to report to the European Commission (DG SANCO) the current developments and concerns in the field of xenotransplantation and to identify issues that may require community-wide action.

Introduction

3. There are several diseases for which the best treatment is the replacement of organs or tissues. The increased success rate of transplantation makes it a more viable treatment option, and transplantation is being used as a treatment for an increasing number of diseases. Furthermore, improvements in public health and advances in general medical care are leading to people living longer thus increasing the group of people that may need transplantation. All these factors lead to a greater demand for organs and exacerbate the current organ shortage for transplantation.
4. Besides allogeneic transplantation (between individuals of the same species) other treatment modalities involve the use of artificial organs and devices (implanted or extracorporeal), the use of tissue engineering, and the use of xenogeneic organs, tissues and cells (from a different species). Artificial organs and devices are not available for all organs and they have various limitations, whereas organ transplantation often provides an acceptable quality and quantity of life. Progress is being made with tissue engineering using material scaffolds on which autologous or allogeneic cells are grown. However, their availability and application in the clinic is mainly limited to skin and bone regeneration, and so the demand for whole organs is not likely to be solved by tissue engineering. Xenotransplantation – the transplantation of animal cells, tissues or organs

into humans, could therefore become an effective alternative to the use of human or artificial materials.

5. Attempts have been made to transplant kidneys and livers from chimpanzees and baboons, and hearts from chimpanzees, baboons, pigs and sheep into humans (Council of Europe 2000), but they were all largely unsuccessful due to an inability to overcome hyperacute rejection. When the donor is not a primate this form of rejection is based on a very rapid reaction against the α -1,3-galactosyl (α -gal) on animal cells, and attempts to overcome it included removal of the reactive circulating antibodies, and prevention of complement activation. Genetic modification of animals (transgenesis) for down-regulation of the α -gal on the cell surface has also been considered (Cozzi et al., 1995, 1997). Whether transgenesis, for instance, in pigs will solve this problem remains to be established, but at the present time the treatment of end-stage organ failure using xenotransplantation of whole organs is considered premature (Cooper et al. 2000).
6. On the other hand, there have been encouraging developments in the area of xenotransplantation of cells, and clinical trials are being carried out (Heneine et al., 1998, Dinsmore et al., 2000). Similar progress is being made for extracorporeal perfusion, where body fluids are 'cleaned' by passing blood from patients waiting for a transplant through animal organs before being returned to the patient.
7. Perhaps of greatest concern is that xenotransplantation carries a significant risk of infection, not only for the recipient but also for the population at large. It is possible that in an immunosuppressed host a xenogeneic infection may occur, involving transmission of pathogens from transplanted animal cells to the human host. Moreover, new diseases may arise in the host caused by hitherto unknown pathogens. In both cases, a disease may be established and transmitted to others in the community. In addition to the risk of infection, there might also be difficulties in recognising and diagnosing such an event at an early stage as such new diseases evolve. Thus the problems involved in xenotransplantation are not only limited to the patient but extend to the public as well.
8. Xenotransplantation, if seen to be a successful therapy, is likely to develop quickly and to be used internationally. Consequently, any xenogeneic disease may well also spread

geographically relatively rapidly, and therefore, there is some urgency to these considerations.

9. Several bodies, national governments, and supranational organisations (e.g. Council of Europe, OECD, WHO) have already made some risk assessments and put forward proposals. The Council of Europe considered xenotransplantation of whole organs, cells and tissues in 1997 and, in the name of the precautionary principle, recommended a ban that was unanimously adopted on 29 January 1999 by the Parliamentary Assembly of the Council of Europe (Recommendation 1399:1999). The recommendation, among other things, called for a legally binding moratorium on all xenotransplantation in humans, including clinical trials. However, European Community wide legislative or regulatory frameworks have not yet underpinned these decisions.
10. In addition to the above concerns, there is not even a mechanism in place to collate and share information between countries. Extracorporeal perfusion and xenotransplantation of cells are being conducted within the European Union and there are signs that it would be an appropriate time to start clinical trials (Platt 1998, Vogel 1998, Onions and Witt 2000, Barker and Polcrack 2001). It is extremely important therefore to re-examine the strategies in place and options available to support and control xenotransplantation as well as to ensure public health.
11. The public health and wider community issues might be better handled by a single approach across the European Union rather than by individual Member States, particularly as the public health implications will not be limited by geographic boundaries. Ethical, social, and religious values and perceptions, are also of importance and may influence the final acceptance or rejection of xenotransplantation as a therapy, but they have not been considered in detail in this report. This Opinion addresses and identifies the scientific issues that are considered important areas on which the European Commission should focus.

Definition

12. For the purpose of this Opinion, xenotransplantation is defined as:

Any procedure that involves the transplantation or infusion into a human recipient of:

- (a) **living cells, tissues, or organs from a non-human animal source, or**
- (b) **human body fluids, cells, tissues or organs that have had ex vivo contact with living non-human animal cells, tissues or organs (e.g. extracorporeal perfusion).**

13. The use of and contact with living animal cells is a crucial part of the definition as non-viable animal materials are regulated by the Medical Device Directive (EC 1993). Non-viable animal tissues and tissue-derived materials commonly used include pig heart valves, bovine bone, calf pericardium, collagen and gelatine. These animal materials are normally subject to several inactivation procedures that minimise the risk of infection. On the other hand, human contact with viable animal cells and the re-introduction of cultured autologous or allogeneic cells or body fluids in a patient represent quite different risks, particularly in regard to cross infection.

Points to consider

Current state of xenotransplantation

14. The history of xenotransplantation started almost a century ago with the transplantation of organs (mainly kidneys from rabbits, pigs, goats, sheep, and non-human primates) into humans (OECD 1999). Although largely unsuccessful, medical advances have now made the use of xenogeneic cells and organs far more plausible as a viable treatment option (Taniguchi and Cooper, 1997). The Working Party on Xenotransplantation of the Council of Europe has prepared a report on the issue, which is out for public consultation (Council of Europe 2000).

Clinical developments

1. Attempts to use whole intact organs have so far failed, usually within the first few days or weeks, so that their transplantation is currently not a real option (Cooper et al., 2000). However, other techniques in xenotransplantation are advancing and clinical trials are already being carried out using extracorporeal liver perfusion and transplantation of animal cells (Patience et al., 1998, Paradis et al., 1999). In addition, there are products

being used in the USA, that are manufactured by *in vitro* co-cultivation of autologous human skin cells with irradiated mouse feeder cells (Epicel™, Genzyme Tissue Repair, Cambridge, MA, USA), and by definition these products fall into the category of xenotransplants. One of the benefits of this approach is the potential to create commercial products for immediate use when needed. In general, the risk of infection from *ex vivo* contact of human and xenogeneic cells is probably lower than xenotransplantation of whole organs in an immunosuppressed host. Nevertheless, the risk is not negligible.

16. As a result of these experiments and treatments the risk for transmission of xenogeneic infections from animals to human recipients exists already. However, specific measures for clinical trials dealing with authorisation, informed consent, registration, surveillance of patients, and those at risk are lacking but could be defined on the basis of Directive 2001/20/EC.

Risk of infectious diseases

17. The risk of infectious disease is mainly dependent on the choice of source animal to be used. Pigs and non-human primates are the two main sources that have been considered to date and each have their advantages and disadvantages. Organs from non-human primates may cause less rejection problems than other species, but these animals are either endangered or relatively unavailable. Furthermore, it would virtually be impossible to set up breeding colonies to produce the numbers that are likely to be required. In addition, because of their phylogenetic relatedness with humans the risk of transmitting infections is relatively high (see below). In Europe, the use of non-human primates when that involves the use of the great apes as source animals is prohibited, except for research purposes (and even that is now being seriously questioned). In the USA there are fewer restrictions, but the Food and Drug Administration (FDA) has retained a ban on transplants from non-human primates (FDA 1999, Butler 2000). Because of these considerations, pigs are the most likely species to be used in xenotransplantation, but they too pose a risk of infection. There is also a risk that pig organs after transplantation may still be susceptible to porcine diseases.
18. An infection, which is the presence of a replicating micro-organism in a host, may induce mild or severe disease, and can often go unnoticed (sub-clinical disease).

Xenotransplantation poses a risk of inadvertently transmitting infection and disease to humans, not only for the recipient but also for the whole human population. It falls into the category of hazard where, although the risk is probably low and the benefit to individuals undoubtedly substantial, the public consequences could be catastrophic (Anonymous 2000).

19. Xenotransplantation has some unique features that may favour transfer of infectious agents from source animals to humans. For example, the normal first line of defence against infection, such as skin and mucosal surfaces are circumvented by transplantation, and furthermore, the recipient would be immunosuppressed. Multiplication in the recipient could result in excretion of the infectious agent, which subsequently could be transmitted to those humans in close contact with the recipient, as well as others in the population.
20. There are numerous pathogens present in non-human primates, and the genetic relatedness of primates with humans suggests that their micro-organisms may be relatively easily transmitted and adapt to their new human host and spread. While all kinds of infectious agents such as bacteria, viruses, parasites, protozoa, fungi and others may be transmitted viruses, at the moment, are the major concern. Several exogenous retroviruses prevalent in humans (such as HIV-1, HIV-2, HTLV-1, and HTLV-2) originate from non-human primate viruses. In addition, there may still be unknown transmissible agents in non-human primates. For these reasons the Working Group of the Council of Europe on Xenotransplantation concluded that non-human primates should not be used as source animals (Council of Europe, 2000). However, the use of pigs also harbours a risk for introducing infection and disease into humans. Recently a comprehensive review described the risks of infection in xenotransplantation with the pig as source species (Muir and Griffin, 2001).
21. Categories of viral infections that theoretically may be transmitted to humans, each of which has its own risk level, are listed below (modified and extended from Günzburg and Salomons, 2000).
 - a) Zoonoses, such as influenza A, Nipah, rabies and others,.

- b) Possible or potential zoonoses, such as encephalomyocarditis, porcine endogenous retroviruses (PERVs), and others,
 - c) Common pig viruses that normally do not infect man, such as classical swine fever, cytomegalovirus, parvovirus, and others,
 - d) Viruses that normally do not infect pigs, but have incidentally been reported to infect pigs, which include lymphocytic choriomeningitis, Hantaan virus, and others (Council of Europe, 2000).
 - e) New viruses that may arise due to recombination of retroviral human and porcine sequences, or due to the formation of pseudotypes, i.e. a hybrid virus carrying the genome of one virus and (part of) the envelope of another, or by re-assortment in the case of influenza viruses.
 - f) Yet unknown viruses. In the last 2 years DNA sequences of three novel different gammaherpesviruses have been reported, indicating there is a chance for the presence of yet unknown pig viruses in pigs.
1. The viruses listed in a) to f) are among the most significant, but there are additional viruses in each category and the non-viral micro-organisms are not even listed. The risks of most of these micro-organisms can be substantially reduced or even eliminated by breeding pigs in a barriered environment, where they would be regularly screened for the absence of infection from a wide spectrum of viruses, bacteria, parasites et cetera. However, detection methods will have to be developed or updated for some pig viruses, particularly for those that are not relevant in veterinary medicine (e.g. for polyoma virus in pigs).
 2. It is obvious that even breeding and keeping pigs under barriered conditions may not exclude hitherto unknown viruses. It is also difficult, if not impossible, to safeguard against novel viruses that emerge from recombination events, and so a major concern is the potential for the occurrence and spread of unknown as well as known animal diseases into man.
 3. Methods to remove PERV from the genome, for example by selective breeding, are not currently available and these viruses pose the most obvious risk at present. While different groups of PERVs have been shown to be present in the pigs' genome and may

inevitably be transferred into the recipient (Patience et al., 2001), this does not imply that it will be detrimental. Infection of human cell cultures by PERVs has been documented (Specke et al., 2001). On the other hand, samples from 160 humans who had been exposed to living pig tissues up to 12 years earlier showed no evidence for PERV infection. Persistent micro-chimaerism (the presence of donor cells in the recipient) was observed in 23 patients without any adverse effect (Paradis et al., 1999), and similar results have been seen in other smaller studies (Heneine et al., 1998, Patience et al., 1998). More recently, Dinsmore et al., (2000) showed that there was no integration of PERV provirus into human peripheral blood mononuclear cells after intracerebral transplantation of fetal neuronal cells in patients with neurologic disorders.

4. However, some animal experiments indicate that the situation may be different when organs are transplanted into humans who are severely immunosuppressed. After transplantation of PERV positive pig pancreatic islets into non-obese diabetic, severe combined immunodeficient mice, viral expression was found and several tissues became infected (Van Der Laan et al., 2000). In contrast, Specke et al., (2001) could not detect productive PERV infection in immunosuppressed rats inoculated with PERVs. From these conflicting results, it is clear that further animal and clinical studies are needed in order to assess the risk of transmitting PERVs and other viruses to humans undergoing xenotransplantation and immunosuppression. In addition, severe immunosuppression by drugs such as cyclosporin may alter the metabolism of other drugs that are used in xenotransplant patients, through interference with the activity of liver enzymes such as the cytochrome P450 system (Dresser et al., 2000).
5. The AIDS (acquired immunodeficiency syndrome) and BSE (Bovine Spongiform Encephalopathy) public health crises have emphasised the need for caution. The European Commission should be aware of this public sensitivity and measures taken to give the public confidence that the risks of xenotransplantation will be thoroughly examined. Furthermore, the results should be made public at the earliest opportunity for information and discussion. However, there is no such thing as zero risk. The endogenous retroviruses seem to be the agents with the highest and as yet unknown risk, especially as patients will be immunosuppressed, and the first barrier to infection (i.e. skin, mucosal membranes)

has already been by-passed. In addition, retroviruses themselves can cause immunosuppression (Denner 1998).

6. There might be a risk to humans receiving an organ from a pig that has been in contact with an infected human. We know relatively little about how human pathogens are dealt with by animals if they do not produce overt disease. They could carry human pathogens for short periods before elimination.
7. It is apparent from the above possibilities that it is imperative to minimise any infection risk by having a quality assurance system in place to ensure that the microbiological status of the source animals is impeccable.

Surveillance

8. The potential for transmission of infection between humans makes the risk of using xenotransplantation a global problem. Management of such risks involves early recognition and identification of disease, and so strategies for early detection, identification and containment of possible infections need to be developed. In this respect, monitoring for adverse effects and reporting to a regulatory authority is essential.
9. As we are dealing with a possible global threat, international cooperation is needed. Information on the conduct and the results of clinical trials should be shared and reported centrally (OECD 1999). The sharing of knowledge is one of the main goals of this registration. Registries and monitoring systems already exist for known “classical” infections and they can be used as an example of how to set up and implement a surveillance system for xenotransplantation. The surveillance of xenotransplanted patients is of importance, but careful statutory regulation of the surveillance is needed as it will have a serious impact on the lives of the patients, as well as others at risk.
10. When more knowledge is gained on the potential pathogens and the extent of the risk posed, patients can be better monitored. It is unclear who should be monitored in addition to the xenotransplanted patient: carers, close relatives, visiting friends, neighbours and others Or whether travel should be limited. Xenotransplanted patients should be identifiable so that if a crisis occurs, e.g. outside of their normal home, the treating

physician may react appropriately in view of the possible hazards involved, with procedures that could exceptionally involve isolation.

11. Another issue is how long should persons be monitored? In a recent overview, a time frame of five years was suggested with a reassessment of the monitoring programme after five years providing there had been no signs of pathogenic virus release (Günzburg and Salomons, 2000). However, it can not be excluded that some diseases may have longer incubation periods.
12. Some of the measures that may need to be taken in a surveillance system may have legal implications as they could be in violation of the Declaration of Helsinki and other guidelines for research on human subjects. In the recent EC directive for conduct of clinical trials, the right of a subject to withdraw from a clinical trial is explicitly stated (EC 2001), and this could be a problem for prolonged surveillance in xenotransplantation clinical trials. As xenotransplantation has implications for public health, it may be that certain rights may have to be modified in such a way that surveillance can be continued. Patients (and others?) could therefore have to agree to waive some of their human rights.
13. In order for the EU to be prepared, it is important that there should be some form of registration of the clinical trials, and collation and exchange of information. An international agency like WHO seems a likely candidate to function as office for the distribution of information to local governments. Registration and surveillance are necessary for xenotransplant recipients and others at risk. This surveillance also extends to the source animals and their husbandry staff.

Ethical considerations for humans

14. Xenotransplantation raises ethical as well as scientific considerations for all those involved. Whilst these will not be discussed in detail they include practical considerations such as obtaining informed consent from the early clinical trial patients, the gaining of consent from non-transplanted persons in contact with the patient for surveillance purposes (including animal handling staff, nursing staff and those dealing with patient samples), archiving of samples, data protection of personal details, dissemination of

results, confidentiality conditions by contributing commercial companies, and even, perhaps, how to handle breaches of agreed contracts when others may be put at risk.

Quality assurance, health and welfare of source animals for xenotransplantation

15. Insofar as the use of animals is concerned all Member States accept that it is ethical for pigs to be killed for food, and so it seems unlikely that using them to save human lives will raise significant ethical issues for the majority of the population. However, those that believe that all animals have a right to a life and a right not to suffer in any way will not accept this view. Animal welfare activists, on the other hand, who do not believe that animals have rights, but rather that humans have a moral obligation not to cause avoidable animal suffering, will wish to be reassured that animals are being kept in the best possible conditions under the circumstances. Thus animals should not be caused avoidable suffering during surveillance procedures, organ and cell procurement, or transport, and that, ultimately, they should be killed painlessly.
16. In relation to the production of transgenic animals, some groups oppose the transfer of human genes into animals. In other areas of research, there have been serious welfare problems in the production of transgenic animals and in breeding them. The welfare of these animals should be monitored by those trained in animal welfare assessment and the results recorded and published.
17. An important discussion in xenotransplantation is the health of the source animal to be used. Choice and selection of individual animals used as sources of organs or tissues should be founded on the concept of quality assurance of all animals present in the original herd, especially their welfare and health status (health is also a welfare problem as poor health can lead to animal suffering). A high health status can be defined as specified pathogen free (SPF) or designated pathogen free (DPF) status, i.e. animals being free from animal pathogens (SPF), or free from animal and human pathogens (DPF). Even a germ free status might be needed.
18. It has been suggested that source animals may have to be kept singly in isolators to maintain their health status. Technically it is possible to do this but it raises serious ethical concerns as pigs are social animals and should be able to interact with other animals.

Rather than barrier the animals at the level of the individual they could be kept in barriered groups in suitably ventilated accommodations (pens) to maintain an appropriate health status. Moreover, early weaning may be necessary and this can cause welfare problems for dam and piglets. These considerations would also apply to other species when used as sources of xenotransplants.

19. Thus, besides the previously mentioned microbiological quality, an appropriately defined quality of the animal production facility is also needed to ensure a high health and welfare status of the source animals.

General considerations

20. Although animals may seem to provide an inexhaustible source of donor organs for transplantation, it is important that the public should not cease to donate their organs, as it is likely that animal organs will not be as well tolerated as human organs. The public should still be focused on the need of altruistic organ donation and its contribution to social cohesiveness.
21. There may also be a socio-economic impact if xenotransplantation is accepted. In the short term it could seriously affect, or be limited by, health care budgets. In the long term, however, there may be significant savings in not having to pay for chronic treatments, and returning people back to a normal life including work.
22. Implementation of a quality assurance system is not only important for the source animals, it should also apply to the centres where procurement of organs and their clinical use is carried out.
23. Experiences from ongoing clinical trials will eventually show whether xenotransplantation is a feasible treatment option. However, from the points considered above it is clear that much more research into xenotransplantation is still needed especially into the potential risks of viral (and other) infections from the animals and between humans. A thorough and continuous risk analysis of xenotransplantation on the basis of the results of both research and clinical trials is indicated.

Concluding remarks and recommendations

24. The first steps in the arena of xenotransplantation have already been taken and cellular therapy and extracorporeal perfusion are under clinical investigation. It will soon be seen whether such therapies are successful. However, regulatory measures are lacking, although some countries do have a legal framework for clinical trials.

25. A legal framework for regulation of clinical trials involving xenotransplantation could be provided by Directive 2001/20/EC of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

26. Alternatives to xenotransplantation of organs, tissues and cells are coming from current research on stem cell technology that may compete with xenotransplantation for possible treatments for conditions such as Parkinson's disease, diabetes and skin replacement. Some experts believe stem cell technology offers a greater chance of success with less concern over immunological problems and biological safety.

27. The following recommendations apply to the therapeutic use of xenotransplantation. Such measures should also apply to routine use of xenotransplantation if and when it is introduced, taking into account the experiences and results of previous clinical trials.
 - I. **In view of the nature of the risks to the public health on an international scale the European Commission should propose the establishment of a centralised regulatory body to oversee the process and to minimise the risks. (Paragraphs 9, 16)**
 - II. **The European Commission should carry out a thorough and ongoing risk analysis of xenotransplantation on the basis of the results of both research and clinical trials. (Paragraph 26)**

- III. Specific measures for clinical trials dealing with authorisation, informed consent, registration, surveillance of patients and those at risk should be defined on the basis of Directive 2001/20/EC. (Paragraphs 16)**
- IV. Appropriate quality requirements related to health status, animal welfare and animal production should be defined and implemented for the source animals to be used in xenotransplantation. (Paragraphs 22, 27, 28, 40)**
- V. Appropriate quality requirements for procurement of organs and their clinical use should be formulated and implemented for centres performing xenotransplantation. (Paragraph 43)**
- VI. Requirements for surveillance should be defined and implemented for the source animals (including husbandry staff), xenotransplant recipients and others at risk. (Paragraph 34)**
- VII. The European Commission should stimulate and support research on detecting and understanding the risks of viral infections with respect to xenotransplantation. (Paragraph 25)**
- VIII. The European Commission should stimulate and support research on detecting and understanding the risks associated with severe immunosuppressive drug therapy, especially relating to interference with other drug therapies. (Paragraph 25)**

References

Anonymous The trials of xenotransplantation. *Nature* 406, 661, 2000.

Barker JH, Polcrack L. Respect for persons, informed consent and the assessment of infectious disease risks in xenotransplantation. *Med Health Care Philos* 4, 53-70, 2001.

Butler D. US decides close tabs must be kept on xenotransplants. *Nature* 405, 606-607, 2000.

Cooper DKC, Keogh AM, Brink J, Corris PA, Klepetko W, Pierson RN, Schmoekel M, Shirakura R, Warner Stevenson L. Report of the Xenotransplantation Advisory Committee of the International Society for Heart and Lung Transplantation: The present status of xenotransplantation and its potential role in the treatment of end-stage cardiac and pulmonary diseases. *J. Heart Lung Transplant* 19, 1125-1165, 2000.

Council of Europe, European Health Committee (CDSP) Working Party on Xenotransplantation (CDBI/CDSP-Xeno) Internet draft (or Discussion draft?), June 2000, Strasbourg, France.

Cozzi E, Tucker AW, Langford GA, Pino-Chavez G, Wright L, O'Connell MJ, Young VJ, Lancaster R, McLaughlin M, Hunt K, Bordin MC, White DJ. Characterization of pigs transgenic for human decay-accelerating factor. *Transplantation* 64, 1383-1392, 1997.

Cozzi E, White DJG. The generation of transgenic pigs as potential organ donors for humans. *Nature Med.* 1, 964-966, 1995.

Denner J. Immunosuppression by retroviruses: Implications for xenotransplantation. *Ann NY Acad. Sc.* 862, 75-86, 1998.

Deng YM, Tuch BE, Rawlinson WD. Transmission of porcine endogeneous retroviruses in severe combined immunodeficient mice xenotransplanted with fetal porcine pancreatic cells, *Transplantation* 70, 1010-1016, 2000

Dinsmore JH, Manhart C, Raineri R, Jacoby DB, Moore A. No evidence for infection of human cells with porcine endogeneous retrovirus (PERV) after exposure to porcine fetal neuronal cells. *Transplantation* 70, 1382-1389, 2000.

Dresser GK, Spence JD, Bailey DG. Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. *Clin Pharmacokinet* 38, 41-57, 2000

European Commission. Directive 2001/20/EC of the European Parliament and of the Council of 4 april 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. OJ L121/34 1.5.2001, Brussels, Belgium.

Food and Drug Administration, U.S. Department of Health and Human Services. Guidance for Industry; Public Health Issues Posed by the Use of Nonhuman Primate Xenografts in Humans. April 1999, (<http://www.fda.gov/cber/gdlns/xenoprim.pdf> (or.txt)).

Günzburg WH, Salomons B. Xenotransplantation: is the risk of viral infection as great as we thought? *Molecular Medicine Today* 6, 199-208, 2000.

Heneine W, Tibell A, Switzer WM, Sandstrom P, Rosales GV, Mathews A, Korsgren O, Chapman LE, Folks TM, Groth CG. No evidence of infection with porcine endogenous retrovirus in recipients of porcine islets-cell xenografts. *Lancet* 352, 1478, 1998.

Muir DA, and Griffin GE. Infection risks in xenotransplantation. Prepared for the Department of Health. Department of Health, London, UK. April 2001.
(http://www.doh.gov.uk/pub/docs/doh/76035_doh_infection_risks.pdf).

OECD Proceedings. Xenotransplantation: International Policy Issues. OECD, Paris, France, 1999.

Onions DE, Witt CJ. Xenotransplantation: an overview of microbiological risks and potentials for risk management. *Rev Sci Tech* 19, 289-301, 2000

Paradis K, Langford G, Long Z, Heneine W, Sandstrom P, Switzer WM, Chapman LE, Lockey C, Onions D, the XEN 111 Study Group, Otto E. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. *Science*, 285, 1236-1241, 1999.

Patience C, Patton GS, Takeuchi Y, Weiss RA, McClure MO, Rydberg L, Breimer ME. No evidence of pig DNA or retroviral infection in patients with short-term extracorporeal connection to pig kidneys. *Lancet* 352, 699-701, 1998.

Patience C, Switzer WM, Takeuchi Y, Griffiths DJ, Goward ME, Heneine W, Stoye JP, Weiss RA. Multiple groups of novel retroviral genomes in pigs and related species. *J Virol* 75, 2771-2775, 2001

Platt JL. New directions for organ transplantation. *Nature* 392, 13-17, 1998

Specke V, Tacke SJ, Boller K, Schwendemann J, Denner J. Porcine endogenous retroviruses: in vitro host range and attempts to establish small animal models. *J Gen Virol* 82, 837-844, 2001.

Taniguchi S, Cooper D. Clinical xenotransplantation – A brief overview of the world experience. In: Cooper DKC, Kemp E, Platt JI, White DJG (eds). *Xenotransplantation. The transplantation of organs and tissues between species*. 2nd Edition. Springer Verlag pp 776-784, 1997.

Van Der Laan LJW, Lockey C, Griffiths BC, Frasier FS, Wilson CA, Onions DE, Hering BJ, Long Z, Otto E, Torbett BE, Salomon DR. Infection by porcine endogenous retrovirus after islet xenotransplantation in SCID mice. *Nature* 407, 90-94, 2000.

Vogel G. No moratorium on clinical trials. *Science* 279, 648, 1998.

WHO. Report of WHO consultation on xenotransplantation. Geneva, Switzerland 28-30 October 1997. WHO/ECM/ZOO/98.2 World Health Organization, Geneva, Switzerland, 1998.

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