Annual report : 1997-1998 / United Kingdom Xenotransplantation Interim Regulatory Authority.

Contributors

United Kingdom Xenotransplantation Interim Regulatory Authority.

Publication/Creation

[London] : Department of Health, 1998

Persistent URL

https://wellcomecollection.org/works/eqm4zxd5

License and attribution

You have permission to make copies of this work under a Creative Commons, Attribution license.

This licence permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See the Legal Code for further information.

Image source should be attributed as specified in the full catalogue record. If no source is given the image should be attributed to Wellcome Collection.

wellcome collection

Wellcome Collection
183 Euston Road
London NW1 2BE UK
T +44 (0)20 7611 8722
E library@wellcomecollection.org
https://wellcomecollection.org

UNITED KINGDOM XENOTRANSPLANTATION INTERIM REGULATORY AUTHORITY

FIRST ANNUAL REPORT MAY 1997–AUGUST 1998


22501828029

WELLCOME TRUST INFORMATION SERVICE
11 JAN 1999
ACC. No. 11269
CLASS:

UNITED KINGDOM XENOTRANSPLANTATION INTERIM REGULATORY AUTHORITY

FIRST ANNUAL REPORT MAY 1997–AUGUST 1998

WELLCOME
LIBRARY
Ann Rep
W028
BA1
U58
1997-98

Contents

Chairman's Foreword

Xenotransplantation raises complex ethical issues. To some, it is a potential solution to the current and ongoing shortage of human organs and tissue available for transplantation. To others, it raises concerns of safety – to the individual and to the wider public; of the efficacy of such procedures; and of the welfare of the animals involved. The UKXIRA exists to consider all of these issues and the ethics which underly them, and to offer advice to the Government on the development of xenotransplantation in the United Kingdom.

The UKXIRA recognises that the public wish to be kept informed of our work. We therefore took the decision, early on in our deliberations, to produce an annual report. That this was an appropriate decision was subsequently confirmed by the publication in July 1998 of the Government's proposals for openness[1] in non-departmental public bodies, which recommended the production of annual reports by all such bodies.

This is the first annual report of the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA). It covers the period May 1997 to August 1998 and reports on the activity of the Authority since its establishment through to the publication of *Guidance on making proposals to conduct xenotransplantation on human subjects*.

The UKXIRA acknowledges that xenotransplantation provokes strong feelings and diverse opinions. Many people have written, both to the Government and the Authority, to express their views on the subject and we encourage people to continue to do so. Public opinion has an important role to play in determining how xenotransplantation progresses and we will continue to take account of all views submitted in overseeing its development.

Following on from this point, a recurring theme of the report is our commitment to wide consultation. *Guidance on making proposals to conduct xenotransplantation on human subjects* is currently out for consultation. Similarly, all proposals for future areas of work will be issued for consultation before being adopted. In addition to consulting widely, we also need to ensure that we consult effectively. If, having read this report and seen the areas on which we intend to concentrate in the coming year, individuals or organisations wish to be included in specific consultation exercises, please contact the UKXIRA Secretariat (for address, see Annex Eight).

Lord Habgood of Calverton

[1] *QUANGOS Opening the Doors* (Cabinet Office, July 1998

Section One Overview of work undertaken

The UKXIRA's work programme

1.1. The role of the UKXIRA is to:

i provide a **focal point** for xenotransplantation activity in the UK;

ii provide a framework for **regulating xenotransplantation** – and in particular to provide a process through which applications to undertake xenotransplantation in humans can be considered and the welfare of source animals safeguarded;

iii assess the scientific and other **evidence** for the safety, appropriateness and efficacy of xenotransplantation, and the justification of any proposed clinical trials.

1.2. The Authority's role as the **focal point** for xenotransplantation issues is important given the number of interests and issues which xenotransplantation brings together – animal and human welfare and ethics, industry, public health, and the other regulatory systems which exist for medicines and medical devices. The Authority exists to advise all government departments and has developed close working relationships with regulatory agencies with an interest in xenotransplantation, and a range of other organisations who have an interest and expertise to offer. The terms of reference for the UKXIRA are included in Annex One of this Report.

1.3. Liaison with other regulatory bodies was an important factor in developing a **regulatory system** for considering xenotransplantation procedures. In July, the Authority published guidance on how to make applications to conduct clinical trials. This outlines both the information any applicants will need to submit and the scrutiny each application will undergo. Details on how to obtain the Guidance are included in Annex Five.

1.4. To give well-founded advice on the general regulation of xenotransplantation, and on particular applications, the UKXIRA needs to be sure that it is acting on the most up-to-date scientific **evidence** and that we are following the best available practice. Porcine endogenous retroviruses have been a matter of particular concern, and were the subject of a workshop hosted by the UKXIRA in August 1998 (see Section 5.10–5.14).

1.5. Another example of the UKXIRA's desire to have access to the best available evidence was the decision to establish a Systematic Literature Review on certain aspects of xenotransplantation. This will concentrate initially on physiology, immunology and infectious disease. It is likely to be some months before there are any results from this Review, but reports will be made available, in both printed and electronic form, in due course.

The UKXIRA's way of working

1.6. Xenotransplantation is a subject which stimulates strong feelings and the public understandably wish to be kept informed of developments. The UKXIRA intends to work in as open a way as possible and so an early decision was taken to present the annual report in an open meeting.

1.7. This report records the activities of the Authority during its first year in three phases: first, the establishment of the Authority; next, consolidating the knowledge base; and then, developing regulatory structures. The report of each phase concludes with an account of meetings the Authority Members and Secretariat held with interested parties, and the conferences and meetings they attended to ensure that they kept up to date with, and contributed to, the latest thinking on xenotransplantation.

1.8. The UKXIRA also launched its website in June 1998. The site contains background information on xenotransplantation, and information about the Authority and its Members. The Guidance on making applications to the UKXIRA can also be accessed through the website. The UKXIRA will be making all publications available in this way. The site is also used to publicise individual events such as the open meeting.

1.9. The UKXIRA website can be accessed at http://www.doh.gov.uk/doh/ukxira.htm.

1.10. The Authority is also committed to wide consultation on its work. We will ensure that the UKXIRA, and those working on its behalf, consult with as many people as possible with an interest in the field, on all work undertaken. Proposals on areas of work will be issued for consultation before being adopted either by the Authority or by the Government. For example, the Guidance on making applications to the UKXIRA was issued for consultation and drafts of proposals on biosecurity standards for animals and surveillance mechanisms will be issued for comment before they are finalised.

1.11. The UKXIRA Members and Secretariat met a wide variety of people in the course of the year. The UKXIRA believes it is important to meet those interested in the field, including industry, and also those who do not support developments in xenotransplantation. These meetings have been immensely useful. The Chairman and Members wish to record their thanks to all those who have given their time and expertise to assisting the Authority.

International issues

1.12. Xenotransplantation is a matter of international interest. Xenotransplantation procedures are currently taking place in the United States, and in the future other countries around the world may initiate programmes. It is recognised that xenotransplant recipients will travel between different countries, whether for treatment or as part of their everyday lives. International co-operation on xenotransplantation is therefore a necessity.

1.13. The aim must be to ensure that xenotransplant programmes, wherever they are undertaken, are carried out to the highest possible standards, to minimise the risk of transferring infection. It is also important to learn from experience of xenotransplantation trials, to collect data which is comparable internationally, and to share information on episodes of specific infectious disease, or other adverse events, should this ever prove necessary.

1.14. The UKXIRA has, since its establishment, sought to further links with the many scientific and medical organisations, and government and regulatory bodies, which exist worldwide. The UKXIRA particularly welcomes the efforts of the World Health Organisation (WHO), the Organisation for Economic Co-operation and Development (OECD), and the United States Public Health Service Agencies in organising conferences which have encouraged international discussion and for their continuing work to facilitate this.

Section Two Background to the UKXIRA

2.1. In late 1995, developments in the biotechnology industry here, in the US, and elsewhere, meant that governments were beginning to consider the ethical and regulatory issues arising.

2.2. But xenotransplantation is not new. The first reported transplants of animal tissues into humans took place early in the 1900s but were impeded due to the inability, at that time, to overcome the rejection processes. The development of immunosuppressive drugs and the success of human to human transplantation prompted a number of xenotransplant experiments in the 1960s. These included two series of experiments to transplant kidneys from baboons and chimpanzees to humans. Since the 1960s, attempts have also been made to transplant hearts from chimpanzees, baboons, pigs and sheep. More recently, there have been attempts to transplant livers, either as a full transplant or as a temporary support.

2.3. In the 1990s, advances in the production of transgenic animals, notably the pig, gave rise to the possibility that the immunosuppression problem inherent in xenotransplantation could be overcome. There is also new and increasing interest in the use of cells and tissues, such as pancreatic islet cells for the treatment of diabetes, or neural cells for the treatment of Parkinson's disease.

2.4. Given these developments, in late 1995 the Government of the time set up an Advisory Group on the Ethics of Xenotransplantation, with the following terms of reference:

> *In the light of recent and potential developments in xenotransplantation, to review the acceptability of and ethical framework within which xenotransplantation may be undertaken and to make recommendations.*

2.5. Professor Ian Kennedy, then Professor of Medical Law and Ethics and Head and Dean of the Law School, at King's College, London, was appointed as Chairman of the Advisory Group. The Membership included experts in transplant surgery, genetics, immunology, moral philosophy, animal welfare, veterinary science and public communication. The Group reviewed and evaluated xenotransplantation, the availability of alternative therapies for those who might benefit from xenotransplantation, and the potential impact on the welfare of individual recipients and on our wider society. During the course of its work the Group conducted a public consultation exercise (receiving over 300 responses) and took advice from a range of experts and those most closely involved in the new xenotransplantation developments. It also held, jointly with the Advisory Committee on Dangerous Pathogens, a workshop on the infectious diseases that might be relevant in xenotransplantation.

2.6. The Advisory Group reported to Government in August 1996. The Group concluded that it could be ethically acceptable to use animals as sources for xenotransplantation if certain conditions were met. These included:

i the type of animal to be used as a source (the Advisory Group advised that the use of primates should not be allowed);

ii further advances in overcoming the immunological problems;

iii the implementation of measures to minimise any risk of infection to human recipients, such as setting standards for the production of source animals;

iv the implementation of systems to monitor the source animals and any human recipients;

v measures to protect the welfare of animals;

vi the banning of sequential removal of tissues from animals;

vii the overall financial impact of xenotransplantation should it become a widely available therapeutic procedure.

2.7. The Advisory Group also recommended that every effort should be made to encourage the expansion of human to human transplantation. But perhaps its most important conclusion was that the evidence available on whether the organ or other tissues would function as indicated, on whether the rejection processes associated with xenotransplantation had been sufficiently overcome and on the infection risks, was not such that a clinical trial could be justified at the time of writing of the report (presented to Government, August 1996).

2.8. The Advisory Group recognised, however, that xenotransplantation was a rapidly developing area. It recommended the formation of a National Standing Committee to ensure that the conditions it had outlined and the issues raised were addressed, and to continue to consider the science of xenotransplantation as new evidence becomes available. This Committee would provide a regulatory framework for xenotransplantation in the UK and the Advisory Group recommended that it should be backed by statute.

2.9. The report *Animal Tissue into Humans* was published in January 1997, together with a Government response which accepted the recommendations it made and which consulted with the general public and interested organisations on the conclusions. However, the Government took immediate steps to implement the Advisory Group's recommendation on the need for a National Standing Committee and also announced the establishment of the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) and the appointment of Lord Habgood of Calverton, formerly Archbishop of York, as Chairman of the Authority.

2.10. Over the next few months, with the assistance of Lord Habgood, the range of expertise required for membership of the UKXIRA was agreed and Members were appointed by the Secretary of State for Health and the Health Ministers of Scotland, Wales and Northern Ireland. The appointments procedure followed the principles outlined in *Guidance on Appointments to Public Bodies* (OCPA, April 1996), published by the Commissioner for Public Appointments. Lord Habgood also provisionally agreed terms of reference for the UKXIRA, based on the conclusions of the Advisory Group on the Ethics of Xenotransplantation. The membership and terms of reference were announced in March 1997.

Terms of reference

The original terms of reference announced in March 1997 were:

> *To advise the Secretaries of State of the UK Health Departments on the action necessary to regulate xenotransplantation, taking into account the principles outlined in* Animal Tissue into Humans, *and worldwide developments in xenotransplantation. In particular to advise:*
>
> *a. on safety, efficacy and any other preconditions for xenotransplantation for human use, and whether these have been met;*
>
> *b. on research required to assess safety and efficacy factors in xenotransplantation procedures;*
>
> *c. on the acceptability of specific applications to proceed with xenotransplantation in humans; and*
>
> *d. to provide a focal point on xenotransplantation issues within government.*

Sub-paragraph (a) was subsequently amended following discussion within the Authority – see paragraph 3.4. The UKXIRA's terms of reference are given in full in Annex One.

Section Three Establishing the Authority May–Oct. 1997

Introduction

3.1. The UKXIRA met for the first time on 19 May 1997 and again on 1 July and 11 August. The aim of these early meetings was to establish the UKXIRA and its working methods as quickly as possible.

3.2. The UKXIRA recognised from the outset that, since this was a new committee dealing with a new area, clear agreement about the role of the Authority and its specific remit, was required – both from the membership itself and from Government. The UKXIRA therefore devoted its first meetings to its working arrangements and its role, in particular in relation to the other organisations that have expertise relevant to the field of xenotransplantation. It also undertook two specific tasks – to consider and advise on the outcomes of the consultation exercise held on *Animal Tissue into Humans* and the Government's response; and to advise on a proposal from the Gene Therapy Advisory Committee.

The UKXIRA's working arrangements

3.3. The UKXIRA agreed that it wished to adopt open working practices and make information about its work available to the public and other interested organisations in the UK and abroad. In particular, an Annual Report should be produced. Other steps were taken to comply with *Non-Departmental Public Bodies: A Guide for Departments* (Cabinet Office and HM Treasury, 1992, updated 1996), including the establishment of a Register of Members' Interests.

3.4. The role of the UKXIRA had been set out by *Animal Tissue into Humans* and provisional terms of reference were drawn up by the Government. The UKXIRA considered the report and agreed that it provided the ethical underpinning for the regulatory work it would put in hand. The terms of reference were also discussed in some detail and it was concluded that these should reflect more explicitly the need to consider animal welfare. A change in these terms of reference was therefore proposed, and later agreed by Government. The sub-paragraph (a) now reads:

> *a. on safety, efficacy and considerations of animal welfare and any other pre-conditions for xenotransplantation for human use, and whether these have been met.*

3.5. The future work programme was effectively set by the terms of reference. A priority was to begin discussions with relevant organisations about suitable regulatory processes through which to assess applications to undertake clinical trials.

The scientific, medical and ethical knowledge base

3.6. The need to keep up to date with the latest scientific, medical and ethical knowledge was also recognised. The collective knowledge base of the membership offers a wide range of expertise but the UKXIRA agreed that wider consultation with those working in the field would also be necessary at regular intervals, through meetings, attending and contributing to conferences, and consultations on topics of particular interest.

Links with other government bodies

3.7. The remit of the UKXIRA is wide and falls across many of the traditional boundaries that exist between animal and human health and welfare. As a result, there are a number of organisations and bodies, within government and outside, whose interests interact with the UKXIRA. The UKXIRA recognised the need for close co-operation to ensure that there was no unnecessary duplication of effort and that appropriate experts were consulted at the proper stages.

3.8. The UKXIRA received early advice on the role and responsibilities of many organisations. The Medicines Control Agency (MCA) and the Medical Devices Agency (MDA) have statutory regulatory roles under which they may be required to consider proposals for certain products which will also need to be considered by the UKXIRA. The Gene Therapy Advisory Committee has a similar advisory role to that of the UKXIRA with regard to

gene therapies. Other organisations with related interests which were contacted included: the Advisory Committee on Genetic Modification; the Advisory Committee on Releases into the Environment; the Advisory Committee on Novel Foods and the Food Advisory Committee; the Advisory Committee on Dangerous Pathogens; the Centre for Applied Microbiological Research; Public Health Laboratory Service; the National Institute of Biological Standards and Control; and the Medical Research Council. The UKXIRA made arrangements to meet those organisations whose roles were most closely related and to keep in touch with those other organisations who had an interest.

The Home Office

3.9. The Home Office, including the Animals (Scientific Procedures) Inspectorate and the Animal Procedures Committee, has responsibility for the Animal (Scientific Procedures) Act 1986, which protects the welfare of animals involved in scientific procedures. The relationship between the UKXIRA and these bodies is therefore important since animal welfare also forms a central part of the UKXIRA's terms of reference. In August 1997, the UKXIRA was pleased to welcome representatives of these bodies: Mrs Judy MacArthur Clark (who had been a member of the Advisory Group on the Ethics of Xenotransplantation) and Professor Robin Dunbar of the Animal Procedures Committee; and Dr Jon Richmond, Chief Inspector of the Home Office (Scientific Procedures) Inspectorate and Mr Steve Wilkes, Head of the Animal Procedures Section at the Home Office. The meeting proved particularly useful in establishing a constructive working relationship and in understanding respective roles and responsibilities.

3.10. Xenotransplantation represents only one area of the use of animals covered by the Animals (Scientific Procedures) Act 1986. The Act controls the use of living animals for "experimental or other scientific purposes" and is regulated in Great Britain by the Home Office and in Northern Ireland by the Department of Health and Social Services. The procedures which the Act seeks to regulate include "any experimental or other scientific procedure which may have the effect of causing a protected animal pain, distress, or lasting harm".

3.11. Pre-clinical research in xenotransplantation largely comes under the regulatory control of the Home Office. Further, permission would be needed from the Home Office to remove tissues from animals for the purpose of transplant into humans. A project licence is required for any programme of work involving regulated procedures on animals. Applications to the Home Office for project licences are considered individually and a cost/benefit assessment is made of each proposal. Clearly, there are links to the work of the UKXIRA. Both the UKXIRA and the Home Office thought it possible that the UKXIRA would be able to advise on specific proposals, in particular on the direction of research.

3.12. Close working between the bodies was essential. A practical illustration of this was Dr Jennings' membership from October 1997 of the Home Office Working Party developing a code of practice for the welfare of animals to be used as sources for xenotransplantation. She was later appointed as a member of the Animal Procedures Committee and her appointment runs from 1 April 1998 for a four-year term.

3.13. The UKXIRA is pleased to have offered advice to the Home Office and the Animal Procedures Committee on research relevant to xenotransplantation, which has assisted in making decisions about applications for project licences received during the year.

The consultation exercise

3.14. Over 50 responses were submitted to the consultation exercise. The views expressed were considered in detail at several meetings of the Authority and detailed advice on each area of enquiry was put to Government. The consultation exercise highlighted a number of areas for particular comment. These were:

i the form and content of any legislation;

ii the remit of the UKXIRA;

iii the use of primates as source animals;

iv the infection risks attached to xenotransplantation, in particular the need to build on the report of the workshop, hosted by the Advisory Committee on Dangerous Pathogens and the Advisory Group on the Ethics of Xenotransplantation;

v the conclusions of the Advisory Group on the immunological and physiological aspects of xenotransplantation.

3.15. In considering responses, the UKXIRA reached a number of conclusions. The call for a clear and non-bureaucratic regulatory framework was acknowledged, as was the need to work within existing structures as far as possible. However, there was also a need to give statutory authority for regulations to be developed as experience increased. The UKXIRA agreed that its remit should have full regard to other regulatory systems and bodies with an interest in xenotransplantation, and undertook to involve all such bodies in appropriate aspects of its work. On infection risks, and immunological and physiological aspects, the consultation exercise stressed the importance of further research, to be assessed through independent peer review systems. The UKXIRA agreed that they would support this as actively as possible.

3.16. The most difficult area of discussion was the use of primates, either as source animals for xenotransplantation or for research. There was particular concern about the welfare of primates, since source animals would have to be kept in very restricted environments to minimise pathogen load. There were also concerns about the relative ease of transmission of specific pathogens from these animals, as compared to animals more distantly related to humans, such as pigs. However, during the consultation exercise, the view was put that at some stage in the future there might be developments of therapeutic value that would only be available if primate tissue was used. If this view was accepted, it would mean that there should not be a ban on primates as source animals. The strength of both arguments was recognised, but the Authority concluded that:

> *...there should be a strong presumption against the use of primates as sources for xenotransplantation. The majority of the Authority recommend a moratorium on such use, but one member remains convinced that primates should never be used as sources for xenotransplantation.*

3.17. A summary of responses to the consultation exercise is available from the UKXIRA Secretariat.

Consideration of proposal submitted to the Gene Therapy Advisory Committee

3.18. The Gene Therapy Advisory Committee (GTAC) is charged with considering and advising on the acceptability of proposals for gene therapy research on human subjects. It considers proposals on ethical grounds, taking account of the scientific merits of proposals and the potential benefits and risks.

3.19. One proposal submitted to the GTAC involved the use of a cloned packaging cell line of mouse origin being placed into the site of a resected brain tumour. In considering this application, the GTAC consulted with the UKXIRA and sought advice on infection risks from the Advisory Committee on Dangerous Pathogens (ACDP). The UKXIRA recognised that this use of animal cells constituted a form of xenotransplantation and therefore came within its remit. In responding to the GTAC, the UKXIRA agreed with the findings of the ACDP that the infection risk associated with this procedure would be very low. The trial was subsequently granted approval.

International Aspects

Meeting on *Cross Species Infectivity and Pathogenesis*, organised by US Public Health Agencies, 21–22 July 1997.

The meeting was organised jointly by the **US National Institutes of Health** (NIH), **Food and Drug Administration** (FDA), **Center for Disease Control and Prevention** (CDC), and **Health Resources and Services Administration** (HRSA). Its purpose was to explore the ability of micro-organisms to cross species barriers and potentially cause disease in humans; in particular, it considered how xenotransplantation might change the traditional barriers of cross-species infection. The meeting was attended by clinicians, scientists, veterinarians, US Government officials, and representatives of pharmaceutical and related industries. Professor George Griffin attended on behalf of the UKXIRA.

Among the main issues identified was whether primates were suitable species to use as sources for xenotransplantation tissue, or whether their use would best be confined to providing a research model. There was a particular concern expressed about the potential for viruses to be transferred from primates to human contacts or xenotransplant recipients. It was known that laboratory workers had been infected with foamy viruses through contact with primates. These laboratory workers were now the subject of a long-term study. Other issues raised included the possibility of pre-emptive vaccination of xenotransplant recipients against specific porcine pathogens and the possibility of research studying those humans who have worked closely with pigs. It was also known that kidney perfusions using porcine tissue had been used for patients in Russia. Research into samples taken at the time of exposure from these patients could prove interesting.

Expert Meeting – *WHO Consultation on Xenotransplantation: Infectious Disease Prevention and Ethical Considerations*, 28–30 October 1997

This expert meeting was organised by the **World Health Organisation**, and was attended by around 40 experts from around the world. Professor Herb Sewell and Rachel Arrundale, Secretary to the UKXIRA, attended on the UKXIRA's behalf. Dr Jeremy Metters, Deputy Chief Medical Officer, attended on behalf of the Department of Health.

The meeting included presentations and updates from around the world, including presentations on the science of xenotransplantation:

i the immunological hurdles to be overcome;

ii the potential risk of infectious disease;

iii the production methods for animals and their ethical implications;

iv the potential impact on different societies of xenotransplantation in health systems with limited amounts of money available.

Presentations were also given on the emerging regulatory response to these issues, in the United Kingdom, Canada and the United States.

The meeting recognised that these matters would be addressed in different ways in different cultures, and presentations included contributions from the Middle East, Asia, Africa, North America and Europe.

The main aim of the meeting was to produce a document on xenotransplantation to serve as a guidance and information source to WHO Member States.

References

Report of WHO Consultation on Xenotransplantation, World Health Organisation, Geneva, Switzerland, doc. number WHO/EMC/ZOO/98.2

Xenotransplantation: Guidance on Infectious Disease Prevention and Management, World Health Organisation, Geneva, Switzerland, doc. number WHO/EMC/ZOO/98.1

Section Four Consolidating the knowledge base Nov 1997–May 1998

Introduction

4.1. Having made initial contact with several related bodies and organisations during the period November 1997 to May 1998, the UKXIRA undertook a programme of meetings, conferences, and other information gathering exercises, to consolidate its knowledge base. During the period, proposals for a regulatory framework through which to consider applications were refined and discussed with relevant bodies. Meetings of the UKXIRA were held on 6 November 1997 and 9 March 1998.

4.2. Meetings were held with representatives of the Advisory Committee on Dangerous Pathogens and of the Public Health Laboratory Service, and Professor John Swales, Director of Research and Development at the Department of Health. Representatives of UKXIRA also attended a range of other conferences and meetings, both to gain information and to contribute views from the UK.

4.3. During 1997, the research groups of Dr Jonathan Stoye and Professor Robin Weiss published in the scientific journal *Nature*[2] [3] . This research did much to heighten awareness of the existence of porcine endogenous retroviruses and showed that they could infect human cell lines in culture. This caused some debate about the implications for the development of xenotransplant programmes which proposed the use of pigs as sources for organs or tissues. Dr Jonathan Stoye and Professor Robin Weiss were therefore invited to present their work to the March meeting of the UKXIRA.

4.4. During this time there was considerable activity on the international front. Two conferences held in the United States did much to further the cause of international collaboration. Contacts made at those conferences led to further meetings between the Authority and representatives of government agencies in other countries. These meetings, together with the interest shown by international organisations, will, it is hoped, form the basis for future long-term international co-operation.

4.5. Effective regulation of xenotransplantation requires the assistance and co-operation of the industry concerned. The UKXIRA considers that meeting, and exchanging views with, those involved in that industry is an essential part of its role. The Authority met representatives of a number of commercial organisations involved in the xenotransplantation industry and was pleased to have had the opportunity to discuss their plans with them.

Links with other government bodies

4.6. Xenotransplantation raises many different issues in a variety of areas. Two such areas are the work of the Advisory Committee on Dangerous Pathogens (ACDP) and the Public Health Laboratory Service (PHLS). As part of its information gathering process, the UKXIRA invited representatives of the ACDP and PHLS to its November meeting. Dr Mike Crumpton, Chairman, and Mrs Eileen Lawrence, Secretary, attended on behalf of the ACDP. Dr Elizabeth Miller, Head of the Immunisation Division, attended on behalf of the PHLS.

The Advisory Committee on Dangerous Pathogens

4.7. The ACDP's role is as a joint Department of Health/Health and Safety Executive sponsored committee whose primary function is to advise and give guidance on infectious disease to workers and others. Dr Crumpton explained that there is not always a clear boundary between occupational health and wider public health, and the ACDP often becomes involved in looking at both. The ACDP also assists in the ongoing task of listing micro-organisms classified by the EC by severity of infection hazard. It has also produced a range of guidance, including *Microbiological risk assessment: an interim report* (HMSO 1996). This considers the general principles of microbiological risk assessment and its application to public health issues.

[2] Patience, C., Takeuchi, Y. & Weiss, R.A., *Nature Med.* 3, 282-286 (1997)

[3] Le Tissier, P., Stoye, J.P., Takeuchi, Y., Patience, C. & Weiss, R.A., *Nature* 389, 681-682 (1997)

4.8. The ACDP also offered to help with further advice on infectious disease issues. The UKXIRA was grateful for this offer and agreed to consider how the ACDP's expertise might best be used.

The Public Health Laboratory Service

4.9. The role of the PHLS is to contribute to the protection of the population from infection, through the maintenance of a national capability for the detection, diagnosis, surveillance, prevention and control of infections and communicable diseases. Dr Elizabeth Miller explained that the PHLS monitors infections in the population, looking at trends, outbreaks, new diseases and measuring interventions. A network of over 50 laboratories is involved in work on reference typing and studies that have a public health function. Information is held centrally by the Communicable Disease Surveillance Centre (CDSC). The PHLS also has particular experience in databases with international links. The development of similar databases is being considered by the UKXIRA for xenotransplantation where the number of xenotransplant recipients is likely to be small.

The scientific, medical and ethical knowledge base

4.10. The UKXIRA met Professor John Swales, Director of Research and Development at the Department of Health, in March, to discuss the establishment of a systematic literature review of issues in xenotransplantation. Professor Swales explained that the Department's Research and Development Directorate was willing to establish and fund a review of relevant literature on xenotransplantation. The UKXIRA agreed that any such work should be in the public domain. The aim would be to produce title lists, abstracts and non-technical summaries, as well as more scientific documents, so that the work would be informative and helpful to a range of audiences. At the time of writing, work is under way to establish the review.

Presentation by Dr Jonathan Stoye and Professor Robin Weiss, 9 March 1998

4.11. The possibility of an infection of animal origin transferring to the human population following a xenotransplantation procedure is a major concern and, of potential infectious agents, porcine endogenous retroviruses in particular have attracted much recent attention. The UKXIRA was delighted that two of the acknowledged experts in this research area, Dr Jonathan Stoye, of the National Institute for Medical Research, and Professor Robin Weiss, Professor of Viral Oncology at the Institute of Cancer Research, were able to attend its March meeting to discuss their work. The discussion confirmed that porcine endogenous retroviruses were an area to be studied closely and that there was little conclusive evidence about how they might behave following a clinical xenotransplantation procedure. This discussion led to the development of the workshop held in August 1998.

International Aspects

Conference: *Developing US Public Health Policy in Xenotransplantation*, organised by US Public Health Agencies, 21-22 January 1998

The meeting was hosted by the **US National Institutes of Health** (NIH), the **Food and Drug Administration** (FDA), the **Center for Disease Control** (CDC), the **Department of Health & Human Services**, and the **Health Resources and Services Administration**. John Dark attended on behalf of the Authority. Rachel Arrundale, Secretary to the UKXIRA, gave a presentation on UK regulatory developments and the role of the UKXIRA.

Conference sessions included:

Pre-Clinical Research and Clinical Trials: Scope and Status A small number of clinical trials in xenotransplantation were already under way in the United States (see table below). No current trials were reported in other countries represented at the conference. The issue of a moratorium on xenotransplantation as a whole had been debated but the general consensus in the United States was that trials should be allowed to proceed.

Infectious Disease Risks Assessment and Management: Current Strategies and Limitation There was a considerable amount of discussion about porcine endogenous retroviruses (PERV) and preliminary data were presented about those patients who had received porcine xenotransplants. No patient showed infection by PERV during the early stages of testing. Further work was being undertaken, most significantly a retrospective study of PERV transmission in humans, involving the analysis of samples from around 160 recipients of xenotransplanted tissue.

Ethical Frameworks. That there were ethical issues associated with xenotransplantation that still needed to be discussed was agreed. One of the most challenging questions posed was: "What should the balance be between expected harms and benefits of transplanted organs in order for clinical trials to be ethically permissible?" It was suggested that potential answers to this question could be found by considering issues of clinical urgency, feasibility, and the potential for scientific discovery. Finally, the impact of, and ethical acceptability of, the regulatory requirements for informed consent of both potential recipients and their close contacts, and the kind of long-term oversight envisaged for these people, needed to be further explored.

International Public Health Policy Perspectives. There were presentations on the regulatory systems being put in place in Canada, the UK and France, and details of the discussions under way on regulatory arrangements in New Zealand and Sweden. The presentation of the UK position explained the background to xenotransplantation work in the UK and outlined the application procedure that was being developed by the UKXIRA. The benefits of international collaboration were discussed. Perhaps the most important of these was international surveillance of xenotransplant recipients. The US was currently developing a pilot National Xenotransplantation Registry, which could serve as a model. The aim was to develop a system to monitor all xenotransplant recipients.

Summary of current xenotransplantation trials taking place in the US

SPECIES	PRODUCT	DISEASE	ALTERNATIVES?
Pig	• hepatocytes • whole liver • transgenic liver • temporary "bridge"	liver failure	human transplantation accepted form of therapy, but shortage of livers
Pig	neuronal cells	degeneratives neurological diseases (Parkinson's and Huntington's)	other treatments available but are not curative for Huntington's; human foetal cells are possible alternatives for Parkinson's
Pig	pancreatic islet cells	diabetes mellitus	other treatments available but are not curative
Cow	adrenal cells	refractory pain in terminal cancer	allotransplantation not standard therapy: unique property of secretion of therapeutic proteins (opioids and adrenergic agents from bovine chromaffin cells)

Meeting with Dr Stewart Jessamine, Senior Medical Adviser at the Ministry of Health, New Zealand, 2 February 1998

The UKXIRA Secretariat met with Dr Jessamine to discuss general issues around xenotransplantation. Amongst the topics discussed were proposals for regulatory requirements, standards for minimising infection risks, surveillance requirements and responses to potential adverse events. There had been a limited small-scale trial in New Zealand involving the implant of pancreatic islet cells as a potential therapy for diabetes but no such work was under way at the present time.

Recommendation: Council of Europe Working Group on Organ Transplantation, 3 March 1998

The Council of Europe Working Group on Organ Transplantation had been asked to consider issues around xenotransplantation. Council of Europe meetings are attended by a Department of Health official. Amongst the recommendations put forward by the working group was that a specific working party consisting of relevant health, scientific and animal welfare representatives be established to consider this subject on a more formal and regular basis. The working party also recommended the initiation of a Europe-wide public debate on the subject, involving all relevant sectors of the Council and other international organisations (including the EU, WHO, OECD). The terms of reference for this group are still being considered at the time of writing. The UKXIRA considers this to be a useful means of promoting Europe-wide co-operation and will follow developments closely.

Conference: *Transplantation Biotechnology: A workshop on international issues including the use of non-human cells, tissues and organs*, 18–20 March 1998

This conference was organised by the Organisation for Economic Co-operation and Development (OECD) in conjunction with the New York Academy of Sciences, and was attended by representatives from medicine and science, industry and government, worldwide. Rachel Arrundale, Secretary to the UKXIRA, attended on behalf of the Authority. The workshop was concerned with international issues in transplantation biotechnology generally but also had a particular interest in xenotransplantation.

The conference drew attention to the importance of further dialogue and international co-operation in xenotransplantation. In particular, it identified the need for further co-operation between the OECD and the World Health Organisation (WHO). Any international co-operative initiative would have several aims including: the development of international databases for xenotransplant recipient surveillance; the development of international standards for risk assessment and for monitoring adverse events; developing standards for animal husbandry to protect animal welfare and biosecurity; and addressing the issue of xenotransplant patients travelling across international borders. The UKXIRA understands that the OECD and WHO are currently in discussion about future initiatives, and welcomes these developments.

Meetings with industry

Meetings with potential applicants

During the period, the UKXIRA met with representatives from the following organisations, both of whom are developing work in the xenotransplant field and who may submit applications to the UKXIRA in the future.

Cell Factors, 7 May 1998

Cell Factors met with Dr Dewdney, Professor Sewell, the UKXIRA Secretariat and also Mr Anthony Taylor, Secretary to the Gene Therapy Advisory Committee. The company is seeking to develop novel therapies utilising expertise in the field of mammalian cell manipulation. The two main therapies currently being developed are for use as a replacement for bone stock (in securing dental implants) and as a treatment for advanced Parkinson's disease.

Imutran, 11 May 1998

The Chairman, Mr Dark, Dr Dewdney, Dr Jennings, Professor Sewell and the UKXIRA Secretariat met with representatives of Imutran to discuss its work in the development of xenotransplantation. Imutran is currently working on an extra-corporeal liver perfusion system for use in the treatment of patients with acute fulminant liver failure for initial clinical trials – prior to moving to solid organ xenotransplantation. Dr Jennings and Professor Griffin had previously visited an Imutran animal facility in November 1997.

Section Five Developing regulatory structures, June–August 1998

Introduction

5.1. June to August 1998 saw the culmination of a substantial part of the first year's work of the UKXIRA, with the publication of *Guidance on making proposals to conduct xenotransplantation on human subjects*. The publication of this work was timed to coincide with the Government's package of measures to regulate xenotransplantation, announced on 30 July.

5.2. In August, the UKXIRA organised a workshop to consider issues relating to porcine endogenous retroviruses (PERVs). This workshop gathered together experts in relevant fields from both industry and academia, and was designed to focus on specific questions about retroviruses. The day proved to be extremely useful to all concerned and a report of the event is currently being prepared. It will be published shortly.

5.3. With the completion of its initial work, the UKXIRA began to take forward several new areas. Work was initiated on the production of guidance on biosecurity standards in facilities where xenotransplant source animals are kept. The aim of this guidance will be to minimise the possibility of infectious disease transmission from source animals. Similarly, the UKXIRA has considered issues around requirements for the long-term surveillance of xenotransplant recipients. Both areas of work will be overseen by steering groups run by UKXIRA Members, and proposals from each will be issued in draft form for consultation with all interested parties. At the time of writing, work in each of these areas continues.

5.4. There were two further meetings with representatives of two overseas committees, both of whom are undertaking reviews of xenotransplantation for their governments. The reviews currently being carried out in Sweden and in Australia are due to be completed in 1999 and are expected to form the basis for future policy on xenotransplantation in these countries. The UKXIRA was pleased to meet these committees and looks forward to hearing the outcome of both reviews.

5.5. Contact with industry during the period included meetings with two organisations involved in the development of xenotransplantation procedures.

Government announcement and issue of Guidance, 30 July 1998

5.6. The Government announced the introduction of further steps to regulate the development of xenotransplantation on 30 July 1998. This announcement also included the outcome of the consultation exercise following publication of *Animal Tissue into Humans*. The UKXIRA's *Guidance on making proposals to conduct xenotransplantation on human subjects* was published on the same day.

5.7. The Guidance outlines the system for submitting applications to the UKXIRA to undertake xenotransplantation procedures within the United Kingdom. It also describes the procedures by which these will be considered. Applications submitted to the UKXIRA will first be considered by a number of expert assessors who will offer advice on particular aspects. Some 30 assessors have been appointed from a variety of relevant fields of expertise. Up to six will be used to consider each application. Their advice will assist the UKXIRA in scrutinising applications before advice is put to UK Health Ministers with whom the final decision will rest. The system is underpinned in England by Health Service Circular HSC 1998/126 (reproduced in Annex Seven) and equivalent guidance in Scotland, Wales and Northern Ireland. No treatments involving xenotransplantation procedures should be commissioned by health authorities, or provided by NHS Trusts, without the prior written approval of UK Health Ministers.

5.8. Furthermore, and only after the UK Health Ministers' approval of any application, responsibility for deciding whether a research proposal should proceed within the NHS lies with the NHS body within whose sphere of responsibility the research would take place, i.e. the proposal must be submitted to the appropriate Local Research Ethics Committee (LREC) to consider its acceptability locally.

5.9. The UKXIRA recognises that there may be ways in which the procedures put in place, and described in *Guidance on making proposals to conduct xenotransplantation on human subjects*, could be improved. The document is therefore open to amendment, and comments/suggestions for improving the process have been invited. All comments received will be considered by the UKXIRA and it is our intention to hold a discussion on these at the Open Meeting in December this year.

Workshop on porcine endogenous retroviruses

5.10. One of the issues which will determine whether clinical trials should proceed is whether the UKXIRA can be satisfied by the available evidence that the risks of transmissible infections are small enough not to outweigh the possible gains such trials might bring. Foremost among these risks are those posed by porcine endogenous retroviruses (PERVs).

5.11. The UKXIRA held a workshop on 6 August to learn more about porcine endogenous retroviruses and to encourage discussion about the significance of existing information. Some fifty leading experts from the United Kingdom and the United States were invited to consider key questions about the current state of knowledge concerning PERVs. The workshop was chaired by Professor Don Jeffries, Professor of Virology and Head of the Department of Medical Microbiology at St Bartholomew's & The Royal London School of Medicine and Dentistry, and member of the ACDP. The UKXIRA wishes to record its gratitude for his help and his expert chairmanship of the day.

5.12. There were three sessions. The first, on *The distribution of PERVs in pigs*, considered whether PERVs existed in all pigs and in all pig tissues. Presentations were made by Dr Paul Le Tissier (National Institute of Medical Research) and by Dr Gillian Langford (Imutran/Novartis). The next session addressed the transmissibility of PERVs, examining both laboratory evidence and evidence from retrospective studies of patients who have received xenotransplanted tissue. Presentations on *Can PERVs be transmitted to humans? Laboratory evidence* were made by Dr Clive Patience (Institute of Cancer Research) and by Dr Carolyn Wilson (Food and Drug Administration, USA); and *Can PERVs be transmitted to humans? Evidence from retrospective studies* by Dr Corinne Savill (Imutran/Novartis), Dr Walid Heneine (Center for Disease Control, USA) and by Alan Moore (Primedica). Finally, the workshop considered what effects transmitted viruses might have on humans. Professor Robin Weiss (Institute of Cancer Research) gave a presentation on *Possible effects of PERVs in humans*.

5.13. Copies of all presentations and details of the discussions following each one will be made available in a full report of the workshop, which is currently being prepared and which will be published separately from this report.

5.14. In brief, the conclusion of the workshop was that endogenous retroviruses probably exist in all types of pigs, that they are expressed in most tissues – although to varying extents – and that it will not be possible to exclude them through "breeding out" in a reasonable amount of time. Given this, attention is now focusing on finding out more about the action of these viruses – how they are transmitted and whether they will cause illness. Limited retrospective studies have been carried out, to determine whether patients who have received porcine tissue have been infected with PERV. Those studies that have been reported show no evidence that the patients have been infected, but the numbers tested are still very small. It remains a matter of judgement for individual countries whether the current state of knowledge justifies a move to clinical trials.

Guidance on biosecurity standards

5.15. If clinical trials in xenotransplantation involving humans are undertaken, it is crucial to minimise the risk of infectious disease transmission. A key area for consideration in this respect are the facilities where source animals will be raised and kept. The UKXIRA considered this topic at its June meeting and agreed to initiate work on the production of guidance

on the levels of biosecurity necessary in such facilities. The aim of the work is to minimise the risk to human health of possible infections from tissue used in any xenotransplantation procedure. The Guidance will set out a framework for the processes and procedures required to ensure best practice in relation to the supply, husbandry and care of animals and derived tissues and organs used in xenotransplantation.

5.16. The UKXIRA has appointed Dr Elspeth Scott of the Home Office Animal (Scientific Procedures) Inspectorate to produce the biosecurity Guidance, directed by a steering group which will oversee the work. It is hoped that the Guidance will be completed by August 1999. However, a draft document will be widely circulated for comment in the spring.

5.17. Clearly, the Guidance which the steering group produces must be compatible with all existing guidelines and regulations, including those on animal welfare. The Home Office Animal (Scientific Procedures) Inspectorate has been charged with developing a *Code of practice on the welfare of xenotransplantation source animals*. Initial discussions have been held with the Inspectorate with the aim of ensuring that the two sets of guidance are compatible with each other and these discussions are set to continue.

5.18. **Steering group membership:**

Dr Janet Dewdney (Chair of steering-group), UKXIRA Member
Dr Maggy Jennings, UKXIRA Member
Prof. George Griffin, UKXIRA Member
Prof. Ian McConnell, Professor of Veterinary Science, Cambridge University
Prof. Peter Biggs, Professor of Veterinary Microbiology, The Royal Veterinary College

Surveillance

5.19. Surveillance, the systematic collection, collation and dissemination of data compiled from separate reports of individual cases, is one of the cornerstones of public health monitoring. Effective surveillance systems for monitoring any human recipients of animal tissues are needed. Surveillance enables:

i prompt action to be taken to treat individuals who are (or may be) infected;
ii investigation of the source of any infection;
iii linking of associated cases that might otherwise be regarded as sporadic; therefore facilitating the investigation of a common source;
iv the existence of an early warning system;
v the plotting of local, regional and national trends;
vi decisions to be made about what future action needs to be taken.

5.20. The UKXIRA has decided that it should oversee the development of a xenotransplantation surveillance system for the UK. The aim of such a system would be to ensure that any patient who received viable animal tissue in the UK would be monitored over a sustained period of time, perhaps even for life. The exact form of such monitoring – the frequency, the clinical symptoms that should be recorded, the serological (blood) testing that should be carried out – will need to be considered. It is envisaged that the results of such testing will be held on some central database. There may also be a need for tissues (for example, blood samples) to be collected from source animals and from xenotransplant recipients, pre- and post-transplant, to allow for research and retrospective analysis. These measures raise ethical concerns, which will be fully explored as part of the work: for example, issues around the confidentiality of the data, and the demands of prolonged surveillance on xenotransplant recipients.

5.21. There are systems in operation which might provide useful models of the database needed for a UK xenotransplantation surveillance system – the Public Health Laboratory Service (PHLS), the Medicines Control Agency (MCA) and the UK Transplant Support Service Authority (UKTSSA). The PHLS system monitors trends in infections in the UK and is used

International Aspects

to identify possible outbreaks and take appropriate action. The UKTSSA system tracks transplant recipients at three months, post-transplant and then annually, and enables analysis of the outcomes of transplants to take place. The MCA system records adverse events or suspected adverse events, related to medicinal products, providing information about adverse reactions and enabling any appropriate action to be taken. All of these elements may be needed in a xenotransplantation surveillance system. The UKXIRA Secretariat met with representatives of each organisation to learn more about their work in this field. This was extremely informative and the UKXIRA is grateful to them.

5.22. Proposals for future progress are being formulated and, at the time of publication, a group is being formed to take this work forward. Proposals will be issued for consultation before being finalised.

Advisory Committee on Dangerous Pathogens

5.23. At the November 1997 meeting with the Advisory Committee on Dangerous Pathogens (ACDP), the ACDP offered further help with advice on infectious disease issues. This offer was subsequently taken up and an ACDP subgroup on xenotransplantation was formed with the following remit:

> *To provide generic advice on the infectious disease risks associated with the different types of xenotransplantation being proposed as therapies, and to provide a report to the UKXIRA.*

5.24. The report was received from the ACDP in August 1998 and is due to be considered by the UKXIRA later in the year. The UKXIRA wishes to thank the ACDP for the work it has undertaken on the UKXIRA's behalf.

Meeting with representatives of the Swedish Committee on Xenotransplantation

At its 6 June meeting, the UKXIRA met with a delegation from the Swedish Committee on Xenotransplantation to exchange views and information about developments in xenotransplantation. The delegation was led by the Committee Chairman, Bertil Persson, formerly a cardiologist and now an MP in the Swedish Parliament.

Scientific developments in a number of areas had prompted the Swedish Government to form and seek advice from a multidisciplinary committee. The Committee on Xenotransplantation, which includes three members of the Swedish Parliament, met for the first time in January 1998. It hopes to make recommendations on possible legislation in spring 1999. No xenotransplantation trials in humans would be conducted until the committee had submitted its report.

One area discussed in some detail was how to engage the public in the debate about xenotransplantation and how to regulate it. The Swedish delegation reported that, as part of an information gathering exercise, a questionnaire had been distributed to 1,500 people in Sweden, seeking views on transplantation generally and on xenotransplantation in particular. At the time of the meeting, some 500 responses had been received, including around 300 from people awaiting kidney transplants. The Swedish delegation also reported that, together with other authorities, it plans to hold a public hearing on xenotransplantation on 20 November 1998.

Meetings with industry

Meeting with Professor Don Chalmers of the Australian Health Ethics Committee

On 10 August 1998, Rachel Arrundale and Martin Houghton from the UKXIRA Secretariat met with Professor Don Chalmers of the Australian Health Ethics Committee (AHEC), which has been asked by the Australian Government to review xenotransplantation and to produce ethical guidelines.

AHEC is responsible for developing guidelines on the conduct of medical research involving humans, other advice relating to health, and for providing assistance to Institutional Ethics Committees (IECs). These are similar to the UK system of Local Research Ethics Committees which advise on the local suitability of specific pieces of research. A specialist sub-group of the national Research Committee has been formed to advise AHEC on the scientific aspects of xenotransplantation.

The decision to conduct a review of xenotransplantation was prompted by the submission of three research proposals to IECs, which sought to conduct clinical trials in humans involving the implantation of porcine pancreatic islet cells as a potential therapy for diabetes. The research applications remain on hold until AHEC's report has been submitted to Australian Health Ministers.

AHEC expects to receive the report of the scientific sub-group by the end of the year, with AHEC's report to Health Ministers following next year. The report is expected to consider ethical aspects and make recommendations for a regulatory mechanism.

Meetings with potential applicants

During the period, the UKXIRA met with representatives from the following organisations:

University Hospital, Birmingham, 1 June 1998

The UKXIRA Secretariat met with representatives of the University Hospital, Birmingham, Liver Unit to discuss their involvement in two projects concerned with the development of bioartificial livers. These are for use in the treatment of patients with acute liver failure.

Genzyme BV, 7 August 1998

The UKXIRA Secretariat met with representatives of Genzyme. The company's interest in xenotransplantation is in the development of a potential therapy for Parkinson's and Huntington's disease. This therapy involves the implanting of foetal porcine neural cells into the patient's striatum, in an attempt to replace and functionally reconstitute regions of the brain that have been destroyed by the disease.

Section Six The future

6.1. The UKXIRA's work to date shows significant progress in a variety of areas. The Authority's advice to the Government on the consultation period following publication of *Animal Tissue into Humans* was reflected in the announcement made on 30 July. That announcement included the issue of the UKXIRA's *Guidance on making proposals to conduct xenotransplantation on human subjects*. A regulatory system for xenotransplantation, with the UKXIRA central to that system, is now in place.

6.2. The focus of much of the UKXIRA's future work will be the consideration of applications to undertake xenotransplantation procedures. Clearly, all applications will require the very closest scrutiny before a decision is made by UK Health Ministers. The process by which applications will be considered – including external expert review and detailed consideration by the UKXIRA before advice is offered to Ministers – is designed to ensure that this is the case.

6.3. Work that has been started on biosecurity, surveillance and the systematic literature review will continue. We expect to issue a draft guidance document on standards for biosecurity for consultation in spring 1999. The consultation will be wide-ranging. The Guidance will be finalised and published in the summer. Work on the development of surveillance mechanisms is also ongoing. We are in the process of appointing a steering group to oversee progress. A timetable for this activity has yet to be drawn up but three specific stages to the work have been identified. The steering group will, initially, consider the requirements for detailing surveillance and biological sampling, and the development of a suitable response mechanism. The third stage, the design of a specification for an information database, will follow after the first two stages have been completed. Again, the UKXIRA will consult widely at appropriate points in the development process.

6.4. New areas for consideration may include the commencement of work on infection control in hospitals, and discussions with professional bodies on training issues. The consideration of ethical issues around xenotransplantation will continue to underpin the Authority's work.

Annex One Terms of reference

To advise the Secretaries of State of the UK Health Departments on the action necessary to regulate xenotransplantation, taking into account the principles outlined in Animal Tissue into Humans, *and worldwide developments in xenotransplantation. In particular to advise:*

a. *on safety, efficacy and considerations of animal welfare and any other preconditions for xenotransplantation for human use, and whether these have been met;*

b. *on research required to assess safety and efficacy factors in xenotransplantation procedures;*

c. *on the acceptability of specific applications to proceed with xenotransplantation in humans; and*

d. *to provide a focal point on xenotransplantation issues within government.*

Annex Two Membership

Chairman

Lord Habgood of Calverton

Members

Dr David Cook
Green College, Oxford

Mr John Dark
Consultant Cardiothoracic Surgeon, Director (Cardio-Pulm. Transplants), Freeman Hospital, Newcastle

Dr Janet Dewdney
Chairman, AdProTech plc.

Mrs Jean Gaffin
Executive Director of the National Council for Hospice & Specialist Palliative Care Service
(Retired September 1998)

Prof. George Griffin
Professor of Infectious Disease, St George's Hospital, Member of Advisory Committee on Dangerous Pathogens

Dr Maggy Jennings
Head of Research Animals Department, RSPCA

Prof. Sheila McLean
Professor, Law and Ethics in Medicine, Glasgow University

Prof. Herb Sewell
Professor of Immunology, Nottingham University, Member of Advisory Group on the Ethics of Xenotransplantation

Remuneration

Fees are paid in accordance with the standard rate for attendance at non-departmental public body health committees, currently set at £131 per meeting for Members and £161 per meeting for Chairmen.

Annex Three Declaration of members' interests

Members are asked to make a statement of any direct or indirect pecuniary interest they consider members of the public might reasonably think could influence the judgements they have to make as part of the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) activities.

The declarations form a register of Members' interests, maintained by the UKXIRA Secretariat. Declarations are updated on an annual basis, but Members inform the Secretariat of any changes as they occur.

Lord Habgood of Calverton
None

Dr David Cook
None

Mr John Dark
Member, Mycophenolate Advisory Board, Roche (F Hoffman-La Roche Ltd). Honorarium, approx £400, paid annually, for two meetings per year
Recipient of Support for Travel, Accommodation and Registration at various meetings connected with transplantation medicine and surgery, from Novartis
Recipient of Support for Travel, Accommodation and Registration at various meetings connected with transplantation medicine and surgery, from Roche (F Hoffman-La Roche Ltd)

Dr Janet M Dewdney
Chairman of a start-up biotechnology company, AdProTech plc. with interests in transplantation

Mrs Jean Gaffin
None

Prof. George Griffin
Consultant, Cambals Vaccines
Consultant, Biocine Vaccines
Member of Scientific Advisory Committee, Edward Jenner Vaccine Research Institute
Member of Physiological Medicine and Infection Board, Medical Research Council

Dr Maggy Jennings
None

Prof. Sheila McLean
Occasional talks to doctors at meetings funded by Glaxo/Wellcome

Prof. Herb Sewell
None

Annex Four Meeting dates

Meetings covered by this report:

19 May 1997

1 July 1997

11 August 1997

6 November 1997

9 March 1998

8 June 1998

Dates for future meetings:

14 September 1998

7 December 1998

1 February 1999

13 April 1999

10 June 1999

2 August 1999

5 October 1999

6 December 1999

Annex Five Publications and references

Guidance on making proposals to conduct xenotransplantation on human subjects. UKXIRA 1998.
(Copies can be obtained from: Department of Health, PO Box 410, Wetherby, LS23 7LL. Fax 01937 845 381)

Report of the workshop on porcine endogenous retroviruses, 6 August 1998.
UKXIRA 1998. (Copies can be obtained from: Department of Health, PO Box 410, Wetherby, LS23 7LL. Fax 01937 845 381)

Summary of *Public responses to the consultation on the report of the Advisory Group on the Ethics of Xenotransplantation, and the Government's response.*
(Copies can be obtained from: UKXIRA Secretariat, Room 311, Wellington House, Waterloo Road, London, SE1 8UG)

Annex Six Government press release

DEPARTMENT OF HEALTH

Press Release

Thursday 30th July 1998

Frank Dobson announces further steps to regulate animal to human transplants

Frank Dobson, Secretary of State for Health, today announced steps to tighten the regulation of the development of animal to human transplants (xenotransplantation).

Following a consultation exercise last year Mr Dobson unveiled a package of measures to encourage the safest development of this technology in the UK:

- A Health Service Circular to the NHS to ensure that all hospitals comply with procedures to make xenotransplantation applications, as set by the UK Xenotransplantation Interim Regulatory Authority (UKXIRA).
- Details from UKXIRA on application requirements for clinical trials in humans. Each application will be scrutinised by the UKXIRA before advice is put to Ministers for a final decision. The UKXIRA will be supported in their work by a number of expert assessors, who will advise on each application.
- An explicit role in considering the welfare of the animals will now be included in UKXIRA's terms of reference.
- The Home Office's Animal (Scientific Procedures) Inspectorate are developing a Code of Practice on the welfare of xenotransplantation source animals.
- Surveillance procedures are being prepared by UKXIRA for any patients who receive animal tissue. The Authority is also developing codes of practice for the levels of biosecurity which need to be maintained in producing the animals. There will be wide consultation on each area of work.
- The UKXIRA is holding a workshop in August to look at one of the key issues – pig retroviruses – involving scientists and industry from the UK, US and Germany.
- The Advisory Committee on Dangerous Pathogens is to set up a working group to look at infection risks of the different types of xenotransplantation therapy being proposed.

The UKXIRA has established a website to give more information about their work.

Mr Dobson said:

"Xenotransplantation is a subject which raises many different views from many different interests. There are patients and patient organisations who are looking to xenotransplantation – and other developments – to provide the therapies they need.

"There are members of the scientific and medical communities and of the general public concerned about the risk to public health from infections transmitted from animals. And there are also concerns about the implications of xenotransplantation for animal welfare. We are pleased to have heard from people representing all of these views and thank them for their interest in helping us further with this work.

"One point emerged from consultation on which there was broad agreement: the need for human organs is clear and efforts to maximise human organ donation must continue. We are committed to promoting and supporting human organ donation and will be launching a new publicity campaign later this year.

"Another clear finding from the consultation exercise was that the regulation of xenotransplantation should have statutory backing. This has the support of those who are concerned about possible risks of infection and of the industry who want a clear regulatory structure to enable them to take their work forward in a responsible manner.

"We take these views seriously and will continue to explore the possibilities for this. In the meantime, the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) will regulate xenotransplantation on a non-statutory basis. I should emphasise however that we stand ready to take action at short notice to prevent undesirable activities if that becomes necessary.

"Trials in xenotransplantation involving humans will only be allowed to take place if and when we are fully satisfied that the risks associated with such procedures are acceptable taking account of all the available evidence at the time.

"I am pleased that the consultation exercise has shown strong support for the UKXIRA. We fully appreciate the diversity of concerns raised by the consultation exercise which the UKXIRA must take into account: the need for protection of potential recipients and of the wider public health; concern for the welfare of animals, and its role in helping the responsible development of xenotransplantation.

"The Authority is working closely with the Home Office to ensure the care and welfare of animals to be used as sources for xenotransplantation is protected.

"One of the most difficult issues raised by the consultation exercise was about using primates as source animals for xenotransplantation. Respondents raised both ethical concerns about using these animals and the theoretical concern that it may be more possible to transmit diseases from these animals than from pigs. Other respondents recognised the need for restraint in the use of such animals, but would not want a complete ban. We have considered this issue carefully. Home Office Ministers have already announced that the use of Great Apes (chimpanzees, gorillas and orang-utans) in scientific procedures – including xenotransplantation – will not be allowed. We also take the view there should be a strong presumption against the use of any other primates as sources for xenotransplantation.

"Discussion about these difficult issues is necessary between all those involved in, or concerned about, xenotransplantation. We will be seeking to encourage discussion about each area of work as it develops. Please continue to let us know your views."

Annex Seven Health service circular 1998/126

Health Service Circular

NHS Executive

Series number:	HSC 1998/126
Issue date:	30th July 1998
Review date:	30th July 2001
Category:	General Management
Status:	Direction

The Secretary of State has powers under a number of provisions in the primary legislation relating to the NHS to give directions to Health Authorities, Special Health Authorities and NHS Trusts. These are legally binding and must be complied with by the recipient. They may be addressed to only one body, or a number of bodies, or all bodies falling within a particular category (such as all Health Authorities).

Clinical procedures involving xenotransplantation

To: Health Authorities (England) – Chief Executives
NHS Trusts – Chief Executives
Local and Multi-Centre Research Ethics Committees – Chairmen

Cc: Health Authorities (England) – Chairmen
NHS Trusts – Chairmen
Independent Healthcare Association – Members

Further details from: Martin Houghton
HSD2C
Room 311 Wellington House
133–155 Waterloo Road
London SE1 8UG

0171 972 4822

Additional copies of this document can be obtained from:

Department of Health
PO Box 410
Wetherby
LS23 7LL

Fax 01937 845 381

It is also available on the Department of Health website at
http://www.open.gov.uk/doh/coinh.htm

© Crown copyright 1998

Health Service Circular *HSC 1998/126*

Clinical procedures involving xenotransplantation

Summary

1. **This Circular announces Directions to the NHS with regard to the commissioning and provision of treatments involving xenotransplantation procedures. The Guidance enclosed with this Circular describes the arrangements under which clinical trials or procedures involving xenotransplantation may be undertaken, and the system for seeking approval to undertake such trials or procedures. The Guidance applies to the whole of the United Kingdom.**

Direction

2. **The Secretary of State for Health, under section 17 of the National Health Service Act 1977, directs health authorities not to commission any treatments for patients involving the use of xenotransplantation procedures without the prior written approval of the Secretary of State.**

3. **The Secretary of State for Health, under paragraph 6 (2) of Schedule 2 to the National Health Service and Community Care Act 1990, directs NHS Trusts to comply with the Direction described in paragraph 2 above.**

4. **The Secretary of State for Health, under paragraph 6 (1) of Schedule 2 to the National Health Service and Community Care Act 1990, directs NHS Trusts not to make accommodation or services available under paragraph 14 of Schedule 2 to the 1990 Act for the purposes of offering treatment involving the use of xenotransplantation procedures without the prior written approval of the Secretary of State.**

Background

5. Xenotransplantation is defined as any procedure that involves the use of live cells, tissues and organs from a non-human animal source, transplanted or implanted into a human or used for *ex vivo* perfusion.

6. The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) was established in 1997 to regulate and oversee developments in xenotransplantation and to advise the UK Secretaries of State for Health on matters relating to xenotransplantation.

7. It is part of the UKXIRA's remit to advise the UK Secretaries of State for Health on "the acceptability of specific applications to proceed with xenotransplantation in humans". Any proposal to undertake a trial or procedure involving xenotransplantation in the United Kingdom should therefore first be submitted to the UKXIRA for consideration. NHS Trusts should note that no trial or procedure should be allowed to proceed on NHS premises without the prior approval of the proposal by the Secretary of State.

8. Xenotransplantation can take a number of forms, including:

   - transplantation of animal organs (such as hearts, kidneys, livers);
   - cell therapies, such as the transplantation of pig neural cells and pig pancreatic islet cells;
   - use as part of a medical device, such as an extra-corporeal liver device utilising viable animal cells; or
   - the use of viable animal cells in gene therapies such as the use of murine cells.

9. Clinical trials or procedures, involving xenotransplantation, may therefore also require the approval or notification of the Medicines Control Agency (MCA), the Medical Devices Agency (MDA) or the Gene Therapy Advisory Committee (GTAC). In general, the first point of contact should be the UKXIRA Secretariat. For gene therapies, the first point of contact should be the Gene Therapy Advisory Committee. Contact details are below.

10. It should be noted that the use of animals in xenotransplantation research or as sources for clinical xenotransplantation requires appropriate authorisation under the terms of the Animal (Scientific Procedures) Act 1986.

Ethics Committees

11. Proposals to undertake research require Ethics Committee approval. Local Research Ethics Committees were advised in HSG(97)23 to ensure that no proposal for a clinical trial of xenotransplantation is considered unless it has first been approved by the UKXIRA.

Applications to undertake clinical trials

12. Details of the procedures for applying to undertake clinical trials involving xenotransplantation are contained in *Guidance on Making Proposals to Conduct Xenotransplantation on Human Subjects*, a copy of which is enclosed with this Circular. The Guidance includes advice on the interaction with the bodies mentioned in paragraphs 9 and 11 above.

13. All enquiries regarding UKXIRA, and applications to undertake clinical trials involving xenotransplantation, should be addressed to:

The UKXIRA Secretariat
Department of Health
Room 313
Wellington House
133–155 Waterloo Road Tel: 0171 972 4822
LONDON SE1 8UG Fax: 0171 972 4852

14. Enquiries involving gene therapies should be addressed to:

The GTAC Secretariat
Department of Health
Room 401
Wellington House
133–155 Waterloo Road Tel: 0171 972 4021
LONDON SE1 8UG Fax: 0171 972 4916

Associated documentation

15. *Guidance on Making Proposals to Conduct Xenotransplantation on Human Subjects*

United Kingdom Xenotransplantation Interim Regulatory Authority, 1998

This Circular has been issued by:

Dr Graham Winyard

Director of Health Services

Annex Eight Contact points

UKXIRA Secretariat
Department of Health
Room 313
Wellington House
133–155 Waterloo Road
LONDON SE1 8UG

Tel: 0171 972 4847/4822
Fax: 0171 972 4852

© Crown Copyright
Produced by Department of Health
14455 HSD 1k 1P Dec 98 SA (SWI)
CHLORINE FREE PAPER