Annual report : 1999-2000 / United Kingdom Xenotransplantation Interim Regulatory Authority.

Department of Health

United Kingdom Xenotransplantation Interim Regulatory Authority

Third Annual Report
September 1999–November 2000

Contents

Chairman's Foreword

This third Annual Report marks an important stage in the life of the Authority. As will be seen, the task of setting up a regulatory framework for xenotransplantation is well advanced. I would like, therefore, to begin by paying tribute to Members of the Authority, those experts who have assisted them, and the Secretariat, for the immense amount of detailed work involved in developing this framework. It is widely seen as a model of its kind. Work in this field necessarily has to be international, and the Authority has every reason to be proud of the contribution it has made to the development of international standards.

Members' initial terms of office expired during 2000, and I am glad to say that all agreed to continue for further, varying lengths of time and were duly re-appointed. Professor Herb Sewell's re-appointment was for just one further year and hence he will step down from the UKXIRA in March 2001. Professor Sewell was also a member of the Kennedy Committee, set up in 1995 to report on the ethics of xenotransplantation and which recommended the creation of the UKXIRA. He has thus served for nearly six years, and made outstanding contributions to the work of both committees. I would like to place on record my personal thanks to him for his efforts.

How far the Authority's regulatory framework will actually be used remains an open question. The year has seen both advances and setbacks in the progress towards safe and successful xenotransplantation. There are intractable problems that have still to be solved and much remains to be done. There are also a number of new developments that may in the long run provide alternative therapies.

Meanwhile, the Authority continues to fulfil its task of collecting information on, and monitoring, all aspects of xenotransplantation. We welcome informed public discussion, and I warmly commend this report as providing a reliable basis for it.

Lord Habgood of Calverton

Section One: Overview

The UKXIRA's task

1.1 The UKXIRA's role is to:

- provide a focal point for xenotransplantation activity in the UK;
- provide a means of regulating xenotransplantation and, in particular, to provide a process through which applications to undertake xenotransplantation in humans can be considered;
- consider the underlying evidence about xenotransplantation developments and to consider whether clinical trials can be justified.

1.2 This report records the UKXIRA's activity over the period September 1999 to November 2000 in each of these three areas.

1.3 Section Two describes the Authority's work as the focal point for xenotransplantation activity in the UK. This includes contact with those involved in the development of the technology, those opposed to its development, and activity internationally.

1.4 The regulatory role is discussed in Section Four. Additional advice that the Authority intends to publish on infection surveillance and on biosecurity is discussed in Section Five.

1.5 The last year has seen numerous developments in the underlying evidence about xenotransplantation. Progress in cloning technology has seen the birth of the world's first successfully cloned pigs. New evidence on the possible effects of porcine endogenous retroviruses (PERV) has provided both a measure of reassurance and further cause for concern. This is discussed in Section Three. The UKXIRA's assessment of progress in xenotransplantation three years after the Authority was established is included at Section Six.

1.6 The UKXIRA Members and Secretariat met a wide variety of interested groups and individuals during the period. These have included regulators from other UK bodies and from overseas, the industry involved in developing xenotransplantation, medical and scientific experts, animal protection advocates, and media representatives. 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.

Section Two: Developments in the UK and elsewhere

Introduction

2.1 Xenotransplantation continues to arouse considerable interest. Over the period of this report, the UKXIRA has had various contacts with other government policy makers, commercial organisations, campaigning groups, the media and international regulators.

Government consultation exercises

2.2 The UKXIRA has been pleased to contribute to consultation exercises on: a draft *Home Office Guidance on the Operation of the Animal (Scientific Procedures) Act 1986;* a Home Office Animal Procedures Committee consultation document *Emerging Technologies and the Animal (Scientific Procedures) Act 1986;* and an Office of Science and Technology document *The Use of Scientific Advice in Policy Making.*

Contact with industry

2.3 The UKXIRA and its Secretariat met a number of organisations interested in the development of xenotransplantation. Brief outlines of these meetings are included below.

Meeting with Circe Biomedical, 21 January 2000

The UKXIRA Secretariat met representatives of Circe Biomedical to discuss progress in the development of the company's HepatAssist bioartificial liver system. Phase I trials had been conducted in three centres in the US and one in France. Phase II trials had commenced in July 1998 and were taking place in various centres in the US and Europe.

The treatment, which utilises porcine hepatocytes, acts as a bridge either to recovery or to transplant for patients with acute liver failure. Future studies may be expanded to examine treatment for other life-threatening forms of liver disease. Current trials involve patients undergoing intermittent treatment for 6 hours. The longest period of treatment so far has been for 8 days but the system allows for up to 14 days.

Meeting with Reneuron, 24 February 2000

Reneuron is developing murine and human neural stem cell lines for implantation into brains damaged by neuro-degenerative diseases such as stroke, Parkinson's, Huntingdon's and Alzheimer's disease. Although its work is still at a very early stage, initial research has indicated that transplanted cells are capable of restoring cognitive function. Rederivation of the murine cell lines would be necessary to conform to regulatory requirements.

Meeting with Genzyme, 28 March 2000

Dr David Cook and Martin Houghton (UKXIRA Secretariat) met representatives of Genzyme to discuss the company's progress in xenotransplant cell therapies for Parkinson's disease. Clinical trials involving the implantation of fetal porcine neural cells into the striatum of patients suffering from Parkinson's disease are taking place in the United States. The meeting also provided an opportunity to discuss Genzyme's work in developing tissue repair treatments, since the processes involved now come within the definition of xenotransplantation adopted by regulatory authorities in the United States.

Meeting with PPL Therapeutics, 5 June 2000

PPL's US subsidiary is undertaking research into the nuclear transfer (cloning) of pigs as source animals for whole organ xenotransplantation. In March 2000, the company announced the birth of the world's first successfully cloned pigs. PPL's xenotransplant strategy involves the genetic modification of source animals to "knock-out" the gene responsible for hyperacute rejection and to introduce three new genes needed to control the causes of delayed rejection.

2.4 The Authority also met representatives of Imutran Ltd on 5 October 1999 to discuss the results of the retrospective study of patients previously treated with living pig tissue. This is discussed further in Section Three. In September 2000, it was announced that Novartis and Biotransplant Inc are to form a new xenotransplantation company based in Boston, US. Imutran is to close with effect from 31 March 2001.

2.5 In August 2000, the Roslin Institute announced that it was to end its research into xenotransplantation.

2.6 The imminent closure of Imutran, coupled with the decision of the Roslin Institute to end its xenotransplantation programme, means that the amount of pre-clinical xenotransplant research undertaken in the UK will be considerably diminished. Those opposed to the development of xenotransplantation may view this as a positive step for their cause. It is not for the UKXIRA to agree or disagree with this view any more than it is our role to promote xenotransplantation research in the UK. We would state only that, in our opinion, scientific research involving the use of animals is best conducted in countries where appropriate regulatory controls are in place to ensure that due regard is given to animal welfare.

Campaigns

2.7 Xenotransplantation provokes strong feelings and diverse opinions. While the current view of the Government is that this technology should continue to be explored in a cautious, step-by-step fashion, it is also recognised that some people for a variety of reasons object to xenotransplantation.

2.8 The UKXIRA has a duty to consider all views expressed and accordingly a standing item is included in all meetings to discuss representations made. Postcard campaigns have been organised by two groups opposed to xenotransplantation. Prior to the UKXIRA meeting on 12 September 2000, a total of 19,606 postcards had been received by the UKXIRA Secretariat.

2.9 In July 1999, the British Union for the Abolition of Vivisection (BUAV) submitted a report containing allegations of the mistreatment of animals at an establishment for breeding research animals. It was claimed that this included pigs bred for xenotransplantation research. The welfare of animals used in scientific research is the responsibility of the Home Office and accordingly that Department undertook

an investigation into the allegations made. No evidence of mistreatment was found. The results of the investigation were conveyed to the UKXIRA in spring 2000.

2.10 In March 2000, the BUAV submitted the results of a public survey purporting to show that 69 per cent of those questioned agreed with the statement that there should be a moratorium on xenotransplantation. Whilst noting the study's findings, the UKXIRA was of the view that the preamble to the question may have unduly influenced the responses received.

2.11 A report prepared by Uncaged Campaigns, *Diaries of Despair*, was forwarded to the UKXIRA in September 2000. The report was based on confidential documents that had been obtained from Imutran Ltd without their knowledge or consent. It makes allegations of serious animal suffering arising from Imutran's research programme and calls on the Home Office to launch a judicial inquiry into the allegations. In response to a Parliamentary Question in the House of Commons on 27 November, the Secretary of State for the Home Department announced that there would not be a judicial inquiry but that the Chief Inspector of the Animals (Scientific Procedures) Inspectorate had been asked to "examine the available evidence relating to compliance with the authorities granted to Imutran for its xenotransplantation work between 1995 and 2000". The UKXIRA will be giving serious consideration to *Diaries of Despair* and the documents on which it is based, though, at the time of writing, both the report and the documents are subject to an injunction preventing their use and dissemination beyond the authorised recipients of the material .

Media contact

2.12 UKXIRA Members have been pleased to co-operate with various television, radio and press requests, including interviews for UK-, US- and Australian- based units.

International aspects

2.13 The fact that xenotransplantation is developing on a global scale highlights the importance of international collaboration. The following paragraphs record various initiatives in which the Authority has participated or of which it is aware.

International aspects – the Council of Europe

2.14 As described in last year's UKXIRA report, in January 1999 the Parliamentary Assembly of the Council of Europe adopted a recommendation which, amongst other matters, called for a moratorium on all clinical trials in xenotransplantation involving humans. The Committee of Ministers of the Council of Europe, in considering this recommendation, decided to establish a Working Party on Xenotransplantation. The Working Party was tasked with drawing up draft guidelines on xenotransplantation. Two UKXIRA Members, Dr David Cook and Dr Maggy Jennings, were appointed to the Working Party.

2.15 The Working Party's preliminary report on *the State of the Art of Xenotransplantation* has now been made publicly available and is open to comment. The report can be obtained through the following Council of Europe website: www.social.coe.int/en/qoflife/ethics.htm. The Working Party has taken the view that

1 The injunction does not prohibit the supply of the Claimant's (Imutran Ltd) Materials or information derived from them to certain "Authorised Recipients", including the UKXIRA.

clinical trials in xenotransplantation should not be performed in any country that does not have appropriate regulations in place. The UKXIRA supports this view.

International aspects – other European bodies

2.16 The European Commission has established an expert committee to offer advice on xenotransplantation.

2.17 The European Committee on Proprietary Medicinal Products (CPMP) and its Biotechnology Working Party are considering the development of a regulatory points-to-consider document on xenogeneic cell therapy medicinal products for human use. The document, as proposed, will include any xenotransplant therapies that also meet the definition of a medicinal product under the European harmonised legislation for medicinal products.

International aspects – WHO Electronic Discussion Group

2.18 In June 1999, the World Health Organisation (WHO) established an Electronic Discussion Group to encourage debate about *international xenotransplantation policy considerations.* The UKXIRA noted the debates that resulted with interest and wishes to express its appreciation to the organisers for their efforts.

Symposium on Xenotransplantation: insights into the development of a novel technology, Bio 2000. Boston, 27 March 2000

Dr David Cook and Martin Houghton (UKXIRA Secretariat) attended the symposium which included speakers from the xenotransplant industry as well as important presentations on newly emerging evidence concerning possible cross-species transmission of porcine endogenous retroviruses.

Fifth European Conference of National Ethics Committees – Science, Communication and Society. Strasbourg, 4-5 September 2000

Mrs Jean Gaffin attended the conference and gave a presentation on the consideration of ethical issues within UK government committees and, in particular, the UKXIRA.

International aspects – collaboration with the US

2.19 Effective regulation of xenotransplantation requires that, where appropriate, regulatory authorities should be able to exchange information about developments in their respective countries. The UKXIRA has therefore entered into an agreement with the US Food and Drug Administration about the exchange of non-public pre-decisional information relating to applications to undertake clinical trials in xenotransplantation. The agreement will clearly be of benefit to both bodies in performing their regulatory roles.

International aspects – regulation overseas

2.20 In the US, an updated draft *Guideline on infectious disease issues in xenotransplantation* was published by the US Public Health Service. Health Canada has published a *Proposed Canadian Standard for Xenotransplantation*. The proposals set out in both documents reflect much of the UKXIRA's own thinking. Reports on proposals for regulatory systems were published in Sweden and Germany. Additionally, the UKXIRA Secretariat has been in contact with government representatives from a number of countries, including France, Israel, the Netherlands, Norway and Russia.

Meeting with Norwegian Xenotransplantation Committee, 25 September 2000

Lord Habgood, Prof. Dark, Dr Dewdney, Prof. Sewell and the UKXIRA Secretariat met representatives of the Norwegian Xenotransplantation Committee to discuss issues around the development of xenotransplantation.

The Norwegian Committee was formed in December 1999 and charged with making recommendations to the Norwegian Government regarding the future of xenotransplantation. The review would cover issues such as the clinical potential of xenotransplantation, alternative therapies, the need for regulation, the associated risks and measures for control, ethics, animal welfare and economic considerations. The Committee's final report is expected to be submitted to Ministers in May 2001.

There are currently no clinical trials taking place in Norway.

Section Three: The knowledge base

Introduction

3.1 The advice that the UKXIRA is able to offer government on xenotransplantation, including advice on its regulatory role of considering individual applications, is dependent on keeping abreast of new developments in the field. The UKXIRA has commissioned three literature reviews to ensure that it is aware of all the available evidence. New research is also helping to inform xenotransplant regulators.

Literature review

3.2 In March 1998, at the request of the UKXIRA, the Department of Health's Research and Development Directorate agreed to commission literature reviews of issues around xenotransplantation.

3.3 The first review, on *Infection Risks in Xenotransplantation*, aims to provide a structured guide to current literature on infection risks in xenotransplantation and highlights relevant issues. The report, prepared by Prof. George Griffin, Professor of Infectious Diseases at St George's Hospital, London, and his research assistant Dr David Muir, has been completed and is currently undergoing peer review. It is expected that the report will be submitted to the UKXIRA early in 2001. Two further reviews – looking at physiological aspects and at legal and ethical considerations – are under way and should be completed in 2002.

3.4 Each of the reviews, when complete, will be published and made available through the UKXIRA website.

Research into porcine endogenous retroviruses (PERV)

3.5 In August 1999, Imutran/Novartis, in collaboration with the US Centers for Disease Control and Prevention, published the results of a retrospective study of 160 patients from around the world who had previously been treated with living pig tissue[2].

3.6 The study examined samples from patients who had been treated up to twelve years previously for various conditions. Pig skin grafts had been used for severe burns and pig pancreatic islet cells for the treatment of diabetes. Other patients had been treated by perfusing their blood outside the body through pig spleens, kidneys, liver cells or liver. The UKXIRA met representatives from Imutran/Novartis on 5 October 1999 to discuss the study's findings.

3.7 No evidence of PERV infection had been found in the 160 patients, including 36 patients who had received immunosuppression treatment and who might therefore be considered to be at increased risk of infection. Twenty three patients were found to have pig cells circulating in their blood (microchimerism) but no active infection was found. Four patients tested positive for the production of *anti-gag* antibodies but were negative for *anti-env* antibodies. The researchers concluded that the antibodies were either pre-existing in the patients or were due to cross-reactivity with an unrelated antigen.

2 K. Paradis *et al.* "Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue", *Science* 1236, vol. 285 (1999).

3.8 The UKXIRA considered that the study provided some useful evidence on the question of infection transmission in xenotransplantation, albeit within the limitations of a retrospective study. That no signs of infection were found provides a measure of reassurance though it is recognised that negative responses cannot guarantee safety.

Research project on xenotransplantation

The Centre for Applied Microbiology and Research (CAMR) is undertaking a research project to investigate the behaviour of porcine endogenous retrovirus (PERV) in animals other than pigs. A report of the first year's progress was forwarded to the UKXIRA in June 2000.

Conclusions are tentative but the finding of PERV-specific DNA in adult mice is consistent with the possibility that the inoculation of human, PERV-producing cells into mice can result in microchimerism, even if the cells are immuno-competent. The finding is comparable to indications in a previous study that patients whose blood had been perfused through a porcine spleen could become microchimeric, apparently over extended periods of time.

The finding of PERV-specific RNA in a few samples from both normal and from immuno-deficient mice provides *prima facie* evidence that transcription of viral genes might also occur. However, it is not known whether this transcriptional activity represents viral replication, or whether it is occurring in residual human cells from the original inoculum or taking place in infected mouse cells. These observations require further investigation.

3.9 In January 2000, the UKXIRA was made aware of the preliminary results of two research groups investigating the possibility of cross-species transmission of PERV. Prof. George Griffin subsequently attended a workshop, organised by Imutran Ltd and held in Gaithersburg USA, to consider the significance of these findings.

3.10 Work undertaken by the research group of Prof. David Onions had indicated that guinea pigs could be infected *in vivo* by subcutaneous injection of PERV. The group's draft report showed that PERV B DNA and genomic RNA could be detected in spleen samples from all guinea pigs infected on two occasions one month apart with cell-free PERV B. Quantitative data indicated that the viral load in the spleens was greater than that injected, leading to the conclusion that productive infection must have incurred. Further, antibodies against PERV gag and env were detected in all immunised animals. These data suggest that *in vivo* cross-species transmission of PERV can occur.

3.11 Studies undertaken by the research group of Dr Daniel R. Salomon at the Scripps Research Institute had looked for PERV infection in immuno-deficient mice that had received xenotransplanted porcine islets. The results demonstrated that pig pancreatic islet cells produce PERV that can infect human cells in culture and mouse cells in multiple tissues after transplantation into immuno-deficient (SCID) mice. However, the research group emphasised that since the pig islets could not be prepared in pure form, the source of PERV in the pig islet preparation was conjectural. These findings were published in the journal *Nature*[3] in August 2000. Further, in addition to local PERV infection at the site of transplantation, distant sites of PERV infection can occur in rafts of transplanted human *cells* (*personal communication, D. Salomon*).

3.12 As both research groups have indicated, the findings from these two studies are not conclusive. It is clear that further studies to confirm the significance of these initial findings are necessary.

3 Van der Laan *et al.* "Infection by porcine endogenous retrovirus after islet xenotransplantation in SCID mice". *Nature* 407, 501-504, 2000.

Section Four: The regulatory role

Introduction

4.1 One of the UKXIRA's primary tasks is to offer advice to the Government on applications to undertake clinical trials involving xenotransplantation procedures in human subjects. The regulatory process by which applications will be considered was launched in July 1998.

4.2 Two further regulatory issues have been under consideration by the UKXIRA: the Authority's role in the regulation of pre-clinical xenotransplantation research on animals, and the definition of xenotransplantation currently used in the UK.

Applications

4.3 In total, three applications to undertake clinical trials have been submitted to the UKXIRA, two of which were recorded in last year's report. A third application was received in October 1999 and underwent scrutiny in accordance with the UKXIRA's published guidelines. It was subsequently returned to the applicant because insufficient information was provided to make an assessment. The application has not been re-submitted.

4.4 **There are, at present, no clinical trials in xenotransplantation taking place in the UK.** Applicants wishing to submit proposals to the UKXIRA are reminded that the Authority has produced a proforma for detailing the information to be included in an application and where in the application specific data can be found. This is reproduced at Annex Four of this Report.

The UKXIRA's role in the regulation of pre-clinical xenotransplantation research

4.5 Scientific procedures involving the use of animals, and hence much pre-clinical research into xenotransplantation, comes under the regulatory control of the Home Office. The relationship between the UKXIRA and the Home Office and its related bodies is, therefore, an important one.

4.6 The UKXIRA has liaised with the Home Office and the Animal Procedures Committee (APC) on matters of concern relating to the development of xenotransplantation. The Biosecurity Steering Group (see Section Five) was able to offer advice and assistance to the Home Office Working Group charged with producing the *Home Office Code of Practice for the housing and care of pigs used as xenotransplant source animals.* Equally, representatives of the Home Office Working Group made valuable contributions to the Biosecurity Steering Group in the production of its report.

4.7 In June 2000, Dr Maggy Jennings and Martin Houghton (UKXIRA Secretariat) met Richard West, Secretary to the Animal Procedures Committee, to discuss the interaction between the two bodies. As a result of this discussion, it has been agreed that a Member of the UKXIRA should be co-opted onto the APC primates sub-committee for meetings in which issues relating to xenotransplantation are due to be discussed. The UKXIRA welcomes this step and looks forward to other initiatives that may help to improve all aspects of the regulation of xenotransplantation.

Definition of xenotransplantation

4.8 The last year has seen increasing focus on the precise definition of xenotransplantation; in particular, whether certain procedures (both pre-existing and newly emerging) require the same ethical and medico-scientific framework as other forms of xenotransplantation.

4.9 The current definition of xenotransplantation used in the UK is:

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.*

4.10 The US Public Health Service and its constituent agencies have been considering this matter for some time and in 2000 agreed to amend the definition of xenotransplantation used in the US to:

Any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (a) live cells, tissues or organs from a nonhuman animal source, or (b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman cells, tissues or organs.

4.11 The essential difference between this and the current UK definition is the element contained in part (b) relating to ex vivo contact. The current UK definition includes ex vivo perfusion but not other forms of ex vivo contact. The US definition therefore encompasses a wider range of possible products/procedures.

4.12 Examples would include procedures that involve the culturing of cells for transplant through contact with a feeder layer of viable animal cells derived from cell lines. Treatments using this type of process include the culturing of replacement skin for the treatment of serious burns victims and for other forms of plastic surgery. Certain gene therapy procedures might also be considered to come within the revised definition though this is an area that is already well regulated in this country by the Gene Therapy Advisory Committee.

4.13 In common with regulatory authorities in other countries, the UKXIRA has been following the US deliberations on this issue with interest. One obvious matter for consideration is the extent of the risk of infectious agent transmission arising from these processes. Typically, they utilise well-established murine cell lines that have been used for a variety of scientific and medical purposes for more than twenty years. Nevertheless, a theoretical risk of infectious agent transmission, however small, exists. The UKXIRA intends to consider this matter further and, in due course, to make a recommendation to the Government about the definition of xenotransplantation used in the UK.

Section Five: UKXIRA steering groups

Introduction

5.1 The UKXIRA agreed, in June 1998, to establish two steering groups to consider issues around, and prepare further advice, on infection surveillance and on biosecurity. The two steering groups have completed their reports. These will be submitted to Government Ministers and published in due course. This section provides summaries of both reports.

Report of the UKXIRA Infection Surveillance Steering Group

5.2 In terms of the long-term follow-up and monitoring required by transplant recipients, xenotransplantation is no different from human (allo)transplantation. Where it does differ is in concerns that recipients, their close contacts and possibly the wider population may be at risk of xenogeneic infection (infections transmitted from animals to humans as a direct result of the xenotransplant).

5.3 A high degree of knowledge exists about the various infectious agents transmitted via human organ transplantation. However, the full spectrum of infectious agents potentially transmis-sible via xenotransplantation, and their possible effects in humans, is still unknown.

5.4 It may be that xenogeneic infections are not transmitted, that they cause little or no adverse effects in humans, or that – as with allotransplantation – only the recipients themselves are susceptible to infection. But, on the basis of current knowledge, we cannot yet rule out the possibility that dis-ease may be introduced into the general population by the xenotransplantation process.

5.5 In view of the theoretical public health risks surrounding xenotransplantation – and as part of an international exercise in raising awareness of the subject – the UKXIRA agreed to establish a steering group to consider requirements for the monitoring and surveillance of potential infections that may be associated with xenotransplantation.

5.6 The report describes a way forward for the monitoring and surveillance of potential infections associated with xenotransplantation including the overall approach and principles, systems and standards, and a model framework for implementation of infection surveillance.

5.7 It also describes measures to ensure that:

- any suspected and/or confirmed xenogeneic infections occurring in recipients and their close contacts and in healthcare and animal workers are:
  - promptly recognised, investigated and managed;
  - rapidly reported to and investigated by the relevant public health and veterinary (animal health) bodies; and
  - reported to the UKXIRA,

- rapid and appropriate control measures are implemented and monitored to prevent spread of infection,
- information is fed back to healthcare professionals, patients, those involved in their care and the public,
- adequate information for evaluation and review of the surveillance system is provided.

5.8 As with allotransplantation, xenotransplant recipients will require regular check-ups throughout their lives and may need to comply with an immunosuppressive drug regime to maintain their health.

5.9 However, lifelong compliance with a post-operative regime for any xenotransplant recipient is likely to require additional conditions. Chief among these are requirements to remain in the surveillance programme even if the xenotransplant is unsuccessful, to have samples taken and stored indefinitely, and to refrain from donating blood and blood products, tissue and organs. A further recommendation, that generated considerable media interest when the report was issued last year as a draft for consultation, is the requirement that recipients should seek advice before having children. Since sexual contact may be a route for infection transmission, barrier contraception is recommended.

5.10 Clearly, such restrictions are unenforceable by law. Appropriate patient selection is therefore crucial. It should be noted that the framework represents the Steering Group's views on infection surveillance within the context of early clinical trials involving limited numbers of xenotransplant recipients. It is not suggested that these requirements would be appropriate for xenotransplantation as a routine therapy and the programme would need to be kept under review in the light of developing knowledge.

5.11 In accordance with the UKXIRA's commitment to public consultation, the document was published for formal consultation in August 1999. The final draft was presented to an international conference in Paris, October 2000, on Xenotransplantation Infection Surveillance (a joint WHO/OECD venture – see below).

Infection Surveillance Workshop, Ottawa, 31 March-1 April 2000

Martin Houghton (UKXIRA Secretariat) attended the Workshop which had been arranged by Health Canada to consider issues around infection surveillance, in particular the need for infection control databases and sample archiving. A report of proceedings will be made available through the Health Canada website in due course (www.hc-sc.ca/hpb-dgps/therapeut).

Joint WHO/OECD Consultation, Paris, 4-6 October 2000

Prof. George Griffin, Dr Amal Rushdy (Infection Surveillance Steering Group) and Martin Houghton (UKXIRA Secretariat) attended this conference which discussed national and international policy considerations on xenotransplantation surveillance. Existing public health surveillance systems were reviewed as possible operational models for the design of xenotransplantation surveillance. The conference also considered what technical, information and logistic elements might be useful in support of effective international xenogeneic infection surveillance.

Report of the UKXIRA Biosecurity Steering Group

5.12 The steps taken to minimise the risk of infectious agent transmission will be an essential factor in the consideration of applications to undertake clinical trials in xenotransplantation. The facilities in which source animals are raised and kept are a key element in this regard.

5.13 For this reason, the UKXIRA established an expert steering group to develop advice on biosecurity considerations for applicants seeking to undertake clinical trials in xenotransplantation.

5.14 The Steering Group's report describes the procedures and processes that the Group regards as current best practice in the production and quality control of xenotransplant cells, tissues and organs to minimise the risk of xenogeneic infections being transmitted to a xenotransplant recipient and, potentially, to the wider population.

5.15 The expected results to be achieved from any programme of biosecurity are:

- the absence of transmission of specified infectious agents from source animals to human recipients,
- the delivery of non-contaminated and viable xenotransplant material through the use of aseptic and efficient harvesting and processing procedures,
- the overall safety and efficacy of xenotransplants; and
- the humane care and use of xenotransplant source animals.

5.16 The Guidance assumes pigs to be the source species for xenotransplantation. However, other species may be appropriate for certain procedures. In these circumstances, applicants will be expected to have regard to the underlying principles set out in the report.

5.17 A further factor for consideration is the welfare of the animals involved. Regulatory responsibility for the welfare of animals used in scientific procedures lies with the Home Office. An expert group from the Home Office Animals (Scientific Procedures) Inspectorate has simultaneously been preparing a Code of Practice for the housing and care of pigs used as xenotransplantation source animals. The Biosecurity Steering Group has worked closely with the Home Office Working Group and the documents are intended to be complementary.

5.18 The Steering Group recognises that the current understanding of all the potential risks of transferring infectious agents as a result of xenotransplantation is incomplete. To eliminate all the possible risks for both recipient and the general population is probably not achievable at present. Moreover, the potential emergence of previously unrecognised organisms has to be borne in mind. The UKXIRA believes that the principles described are sensible and appropriate precautions in the light of current knowledge.

5.19 In accordance with the UKXIRA's commitment to public consultation, the document was published in draft form for public consultation in September 1999. The report is, we understand, being used by a number of countries as the basis for their own policy development.

5.20 **The UKXIRA wishes to express its gratitude to Members of the Infection Surveillance and Biosecurity Steering Groups and to all those who contributed to the production of the reports.**

Section Six: Review of progress in xenotransplantation

Introduction

6.1 The UKXIRA has now been in existence for some three years and Members have completed their initial terms of appointment. This is therefore a suitable time to review the progress made in the development of xenotransplantation.

The organ shortage

6.2 There is currently, and will continue to be, a shortage of human organs and tissue for transplantation. Figures published by the UK Transplant Support Service Agency (UKTSSA)[4] indicate that at the end of 1999 more than 6,700 people were awaiting a solid organ transplant.

6.3 Improved systems for organ retrieval, emerging technical advances such as the development of artificial organs and tissue engineering, together with xenotransplantation are all *potential* solutions to the shortage – as are greater public awareness of the organ donor programme and a proactive approach to procurement. The UK is currently developing programmes to improve donation rates.

6.4 The view has been expressed by some that, rather than pursue complex technologies such as xenotransplantation, a simple and more effective measure to increase the number of organs available for transplantation would be to introduce a system of presumed consent, commonly known as "opt-out". It is true that some European countries with opt-out systems have better donation rates than the UK. But there is no clear evidence that opt-out is the sole factor. Different cultural attitudes, greater provision of intensive care beds, more aggressive and comprehensive procurement programmes, and road death rates all play a part. Some countries with opt-out have lower donation rates than the UK.

6.5 Clearly, healthier lifestyles would also do much to alleviate the need for transplants. However, many conditions that lead to the need for transplants cannot be prevented simply through leading a healthier lifestyle. The fact remains that human organ and tissue transplantation alone is unlikely ever to be sufficient to meet demand.

The development of xenotransplantation

6.6 In considering progress in xenotransplantation, it should be remembered that the technology encompasses a variety of different techniques for the treatment of differing conditions. Within the current definition of xenotransplantation, these can be broadly categorised as: i) whole-organ xenotransplantation; ii) cell transplant therapies, and iii) extracorporeal systems.

6.7 Furthermore, the research itself falls into distinct areas. A brief outline of the efficacy – in terms of overcoming rejection and in increasing survival times – for each category of xenotransplantation is described below. The question of safety applies to all types of xenotransplantation procedure and this is covered separately.

4 *Transplant Activity 1999*, UKTSSA. Note: On 12 July 2000, the UKTSSA's name was amended to UK Transplant.

Whole-organ xenotransplantation

6.8 It is perhaps the nature of the subject that the category that has received the most media attention, whole-organ xenotransplantation, should be the one in which progress appears to have been most problematic.

6.9 Initial research into overcoming the problem of organ rejection adopted a "step-by- step" approach. Public statements by researchers, that the initial hurdle of *hyperacute rejection* (HAR) had been largely overcome, led certain quarters of the media to anticipate a move to clinical trials in the near future. In fact, it appears that other subsequent forms of rejection have still to be overcome. The overall optimal immunosuppressive regime remains unclear.

6.10 Subsequent research has moved towards a broader strategy for the prevention of rejection, notably through the application of new cloning and genetic modification techniques. It is hoped that rejection problems may be overcome through the genetic modification of source animals to "knock-out" the gene responsible for HAR and the inclusion of new genes needed to control later rejection. This approach appears promising, at least in theory, but is still in the very early stages.

6.11 Survival times in animal (primate) models do not yet provide substantive data that xenotransplanted organs are capable of sustaining life in humans. Researchers have indicated that this is related more to the inability to optimise immunosuppresive regimes rather than problems of physiology. Nevertheless, the absence of data is a concern, not least because such data will only be obtained through further animal research.

6.12 In summary, the evidence of efficacy has not advanced at the rate predicted when the UKXIRA was established some three years ago. Clinical trials involving whole organs are clearly still some way off.

6.13 Meanwhile, other approaches to organ repair or assistance are under development. For example, new small impeller-type heart assist devices have just started clinical trials. Initial results[5] show promise. Furthermore, developments in tissue engineering techniques aimed at implanting new myocytes (cardiac muscle cells) into damaged hearts are close to clinical trial. Both developments may rival xenotransplantation as options for the management of end stage heart failure (though, as with xenotransplantation, it is likely that further research involving animals will be required).

6.14 For other organs, the demand for livers can generally be met from the human donor programme though organs are sometimes required urgently in cases of acute liver failure. Artificial livers, offering the potential for short-term support, are currently undergoing clinical trials (see paras 6.21–6.22). Improved procurement and the use of non-heartbeating donors may alleviate the pressure for renal transplantation over the next few years.

6.15 It seems, therefore, that the likelihood of whole-organ xenotransplantation (particularly for heart transplantation) being available within a clinically worthwhile time frame may be starting to recede.

Cell transplant therapies

6.16 Greater progress has been made in the development of cell transplant therapies. Potential treatments for conditions such as Parkinson's disease, Huntingdon's disease, stroke, epilepsy, spinal injury and diabetes are under development and in some cases clinical trials have already commenced abroad.

5 *Westaby et al.* "First permanent implant of the Jarvik 2000 heart", *Lancet* vol. 356. 9 Sept. 2000.

6.17 Within the last five years, small-scale clinical trials have been conducted involving the transplantation of porcine fetal neurons into patients with Huntingdon's disease, epilepsy and patients who suffered a stroke. Similarly, small-scale studies involving the transplantation of porcine fetal islet cells have previously been performed for the treatment of diabetes. A trial involving the placement of encapsulated bovine cells into the spinal canal of terminal cancer patients with morphine-resistant pain, has also been conducted.

6.18 Since 1995, clinical trials involving the transplantation of fetal porcine neural cells into patients with Parkinson's disease have been conducted in the United States. We understand that a further clinical trial is due to commence in 2001.

6.19 The problems of rejection, inherent in whole-organ xenotransplantation, do not appear to represent such a major hurdle with these forms of treatment. Immunosuppresive therapy as used in allotransplantation seems to be sufficient. Some anecdotal evidence of improvement in patients has been reported, notably in the treatment of Parkinson's disease. Although evidence of the efficacy of such treatments is by no means conclusive at this stage, it seems fair to say that these avenues are worthy of continued exploration.

6.20 Stem cell technology[6] may yet provide alternative solutions to any or all of the conditions mentioned above. One obvious advantage of the stem cell approach is that it eliminates the possibility of cross-species infection transfer. It also circumvents the ethical question of using animals as "spare parts", though it does, of course, raise ethical dilemmas of its own such as the use of tissue derived from human embryos. Research into stem cell technology in the UK has, in the last month, been approved by Parliament. But even so, there is still a question of timescale, and opinion is divided as to how long it will be before stem cell therapies are sufficiently advanced to proceed to clinical trials. Xenotransplantation cell treatments may yet offer hope to patients for a period while other technologies are in development.

Extracorporeal systems

6.21 Bioartificial liver devices, in which the patient's plasma is passed through encapsulated porcine hepatocytes, offer support for patients with fulminant liver failure. The technique may be used either as a bridge to liver transplantation or to provide temporary assistance while the patient's own liver recovers. Some clinical trials have taken place and further trials are ongoing in the US and Europe.

6.22 Some patient improvement has been reported in trials so far undertaken but again the evidence is not conclusive. Furthermore, similarly functioning devices that utilise human cell lines are now undergoing trials and early reports have been encouraging. If success can be confirmed, a device utilising human cell lines would obviate the need to use porcine cells.

Safety

6.23 Uncertainty about the safety of xenotransplantation continues to be a significant obstacle. The potential for infectious agents to be passed from source animal, via the transplant, to human recipient and from the patient into the wider population is still a major concern. The breeding of source animals in appropriate biosecure facilities can eliminate many of the obvious agents of concern. But the question of, as yet, unknown infectious agents remains as does the question of agents that cannot be eliminated from source animals by biosecurity controls – in particular the porcine endogenous retrovirus (PERV).

6 See *Stem Cell Research: Medical Progress with responsibility. Report of the Chief Medical Officer's Expert Group reviewing the potential of developments in stem cell research and cell nuclear replacement to benefit human health.* Department of Health, June 2000.

6.24 Since the establishment of the UKXIRA, much new evidence has emerged. As discussed in Section Three of this Report, in 1999 Imutran/Novartis, in collaboration with the US Centers for Disease Control and Prevention (CDC), undertook a retrospective study of 160 patients from around the world who had previously been treated with living pig tissue. That the study found no signs of PERV infection provides a measure of reassurance but negative responses can never guarantee safety. Further, since the study was published, new, more sensitive assays have been developed. The findings from studies using these assays inevitably bring into question the reassurance offered by the Imutran/Novartis–CDC study.

6.25 Various study groups have in the last year reported evidence of cross-species transmission of PERV, two of which (Salomon *et al.* and Onions *et al.*) are discussed in Section Three. The significance of these findings is difficult to assess. For example, evidence of infection in the recipient species does not necessarily imply that the recipient will suffer any adverse effects. Similarly, evidence from small animal models is not necessarily a reliable indicator of the effects that could be expected in a human recipient. Further research is needed before any firm conclusions can be drawn.

6.26 Whether the *same* risk of infectious agent transmission applies to all forms of xenotransplantation remains a matter of debate. It may seem logical to suppose that a permanent whole-organ xenotransplant represents a greater potential for infectious agent transmission than, for example, the temporary passage of fluid through a barrier-protected membrane. But it has to be remembered that a single cell, or a single viral particle, may present an infection risk. Until further evidence comes to light, the UKXIRA considers it prudent to assume that all xenotransplantation procedures carry a risk of some degree.

Other considerations

6.27 The fact that xenotransplantation is developing globally underlines the need for international standards in its regulation. The UKXIRA has worked closely with a number of national and international organisations including: the US Food and Drug Administration and other US public health agencies, Health Canada, the World Health Organisation, the Organisation for Economic Co-operation and Development, the Council of Europe, the European Commission and the European Medicines Evaluation Agency.

6.28 Campaigning groups opposed to xenotransplantation have called for a moratorium on clinical trials. The UKXIRA does not support this view. Until clear evidence becomes available on the infection risks posed by xenotransplantation, the UKXIRA will assess the risk posed by particular procedures individually. Any applications received will be reviewed on a case-by-case basis – taking account not only of the infection risks involved but also evidence of efficacy and the ethical and animal welfare considerations involved.

Summary

6.29 Some progress towards xenotransplantation as a clinical therapy has been made in specific areas such as cell therapies for the treatment of Parkinson's disease. Although alternative therapies are in development, xenotransplantation may still offer the prospect of a viable treatment within a worthwhile time frame. However, on the basis of current evidence, whole-organ xenotransplantation, as a solution to the ongoing shortage of organs for transplant, appears still to be some way off.

6.30 The risk posed by infectious agent transmission, both to the xenotransplant recipient and to the wider population, remains unquantifiable. Further research, particularly into the behaviour of endogenous retroviruses, is required. Until such time as research is able to provide more definitive answers on the safety of xenotransplantation procedures, it is prudent to assume that all forms of xenotransplantation carry a risk of some degree.

6.31 Individual applications to undertake xenotransplant procedures in the UK will be considered on a case-by-case basis.

Annex One: Terms of reference

UK Xenotransplantation Interim Regulatory Authority (UKXIRA)

To advise the Secretaries of State for Health, Northern Ireland, Scotland and Wales on the action necessary to regulate xenotransplantation, taking into account the principles outlined in Animal Tissues into Humans, *and worldwide developments in xenotransplantation. In particular to advise:*

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;*

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.*

Biosecurity Steering Group of the UKXIRA

To specify the biosecurity conditions for each stage in the xenotransplantation procedure which minimise the risks to human health from infections and other disorders resulting from the handling of source animals or as a consequence of the transplantation process.

To give priority to the consequences of the use of pigs as source animals but to address issues which might arise from the use of other species.

To liaise with the Home Office to ensure, as far as possible, that the biosecurity requirements which minimise the risk to humans are compatible with the Home Office Code of Practice relating to the housing, husbandry and care of source animals for use in xenotransplantation.

To ensure familiarity with all appropriate and relevant legislation, codes of practice and guidance notes relating to xenotransplantation.

Infection Surveillance Steering Group of the UKXIRA

With reference to those areas of the UK Xenotransplantation Interim Regulatory Authority's (UKXIRA's) terms of reference that seek to maximise the safety of xenotransplantation procedures and the acceptability of specific applications;

to propose the overall approach and principles, and provide guidance for monitoring and surveillance of potential infections which may be associated with xenotransplantation.

Annex Two: Membership

UKXIRA

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 M. DEWDNEY	Deputy Chairman and non-executive Director of AdProTech plc.
Mrs Jean GAFFIN	Trustee of St Luke's Hospice, Brent and Harrow Non-executive Director, Harrow and Hillingdon Healthcare NHS Trust
Prof. George GRIFFIN	Professor of Infectious Disease, St George's Hospital
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

Remuneration

Fees are paid in accordance with the standard rate for attendance at non-departmental public body health committees, set at £135 per meeting for Members (£139 from 1 July 2000) and £168 per meeting for the Chairman (£173 from 1 July 2000).

Biosecurity Steering Group Membership

Dr Janet Dewdney	(Chair of Steering Group), UKXIRA Member
Prof. Peter Biggs	Professor of Veterinary Microbiology, The Royal Veterinary College
Prof. George Griffin	UKXIRA Member
Dr Maggy Jennings	UKXIRA Member
Prof. Ian McConnell	Professor of Veterinary Science, Cambridge University
Dr Elspeth Scott	(Consultant to the Steering Group) Home Office (Scientific Procedures) Inspectorate
Martin Houghton	(Secretary) UKXIRA Secretariat

Infection Surveillance Steering Group Membership

Prof. George Griffin	(Chair of Steering Group), UKXIRA Member
Dr David Cook	UKXIRA Member
Ms Sarah Elliston	Institute of Law and Ethics in Medicine, University of Glasgow
Mrs Jean Gaffin	UKXIRA Member
Dr Mary O'Mahony	Deputy Director, Communicable Diseases Surveillance Centre, Public Health Laboratory Service
Dr Philip Mortimer	Central Public Health Laboratory
Prof. David Oliveira	Professor of Renal Medicine, St George's Hospital Medical School
Dr David Paton	Central Veterinary Laboratory
Dr Amal Rushdy	Communicable Diseases Surveillance Centre, Public Health Laboratory Service Medical Secretariat, Advisory Committee on Dangerous Pathogens (up to October 1999)
Ms Kate Darwin	UKXIRA Secretariat
Mr Martin Houghton	UKXIRA Secretariat

Annex Three: Declaration of 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.

	Declared Interests
Lord HABGOOD of Calverton	None
Dr David COOK	None
Mr John DARK	Clinical research supported by Roche
	Costs of attending various scientific meetings met in part by Novartis and Roche
	Honorarium for editing meeting review on behalf of Roche
Dr Janet M. DEWDNEY	None
Mrs Jean GAFFIN	Non-Executive Director, Harrow and Hillingdon Healthcare NHS Trust
	Expenses as member of Appraisals Committee, National Institute for Clinical Excellence
Prof. George GRIFFIN	Consultancy fee from Pharmacia and Upjohn paid to St George's Hospital Medical School
	Consultancy fee from Microscience paid to St George's Hospital Medical School
Dr Maggy JENNINGS	Full-time employment with the Royal Society for the Prevention of Cruelty to Animals (RSPCA)
Prof. Sheila MCLEAN	None
Prof. Herb SEWELL	None

Annex Four: Proforma for use by applicants to the UKXIRA

Proforma for completion by applicants seeking to undertake xenotransplantation procedures in thE UK

All applications to the UKXIRA should include detailed information on relevant systems and documentation under the following headings: **SUMMARY DETAILS, PRETRIAL DATA, TRIAL PROTOCOL, BIOSECURITY** and **INFECTION SURVEILLANCE.**

Applicants should indicate the page number(s) of the relevant documentation against each section.

Summary Details

Project title, summary of proposal, applicant's name, sponsor's name, site(s) of clinical trial, proposed number of patients, submission date to UKXIRA, first/second application. A summary flowchart is a useful aid to illustrate the main activities, sites and the responsible parties for sourcing, transplant removal, manufacturing and patient implantation. A statement is required on the National and European regulatory status of the finished product or tissue/organ and the Quality Assurance programme.

Doc Refs

Pretrial Data

Physiological, immunological and pharmacological data on the cell/organ transplant must be available and professionally evaluated before it enters a clinical trial. All existing research data should be collated, reviewed and considered in detail. In particular, this should address the current state of knowledge on the potential for infection of porcine endogenous retroviruses (PERV), with a detailed risk analysis for the patient and the community as a whole. The pre-trial data should contain comprehensive information that is relevant to the application.

Doc Refs

Trial Protocol (1)

General information project title, clinical investigators, other participants or contributors (animal breeders, surgical team, nurses, statisticians, etc) with details of training, experience and qualifications, the sponsor's name/address, the clinic/department for the trial, objectives and justification for the trial (including an assessment of the likely benefit to the patient and possible benefits to other patients in the future), the knowledge and issues of the technology and a summary of the systematic review of the published literature.

Doc Refs

General Design specification of the trial type, description of the randomisation method, the trial design and specification of other bias-reducing factors. The start and end date for the trial, justification for the timescale, the expected duration of the treatment. Rationale for patient selection (including age, sex, ethnicity, groups, prognostic factors), statement of diagnostic admission criteria, criteria for inclusion, pre-admission exclusions, and post- admission withdrawals of patients from the trial. Product labelling shall include the words "For Clinical Trial Only", the name of the clinician responsible and the trial site.

Doc Refs

Treatment descriptive text (with illustrative diagrams) of the product treatment to be used (with justification of the cell quantity in the case of cell transplantation), treatment(s) applied to other group(s) or control period(s), procedure of application, site of application, treatment period for the transplantation and its current comparative treatment, rules for the use of concomitant treatment, measures for safe handling of the transplant, measures to control and promote adherence to prescribed instructions (compliance).

Doc Refs

Law/Ethics legal and ethical considerations of the trial. Comprehensive details and procedures on information to patients (including relatives, contacts, friends), system for obtaining consent and information on compensation.

Doc Refs

Assessment specification of the parameters to monitor the effects, description of measurement and recording of these effects, times and periods of recording, description and purpose of special analyses or tests to be carried out (eg laboratory, clinical, radiological).

Doc Refs

Adverse events methods and systems of recording adverse events, provisions for dealing with complications, where the information code will be kept and its access in cases of emergency, details for reporting adverse events, by whom and to whom, and how fast the reports will be submitted.

Doc Refs

Handling of Records procedures for handling and processing records of effects/adverse events under study, procedures for keeping special patient lists and records for each individual in the trial. Methods to permit easy identification and the retention of report forms.

Doc Refs

Evaluation a specified account of how the response should be evaluated. Methods of computation and calculation of effects, how to report on subjects withdrawn from the trial, quality control of methods and evaluation procedures. Description of statistical methods, number planned, reason for choice of sample size, including reflections on the power of the trial and clinical justification, the rules for the termination of the trial.

Doc Refs

Finance/Insurance all financial aspects in conducting and reporting the trial, as well as the long-term surveillance and monitoring, shall be arranged and clearly specified. Patients/volunteers taking part in the trial should be satisfactorily insured against any injury caused by the trial. The liability of all the involved parties (ie investigator, sponsor, manufacturer, hospital, clinician) must be clearly defined and understood before the start of the trial.

Doc Refs

Biosecurity (2)

Production animal species, location, lineage, facilities, welfare, feeding practices, identification of natural pathogens, health monitoring, vaccination programme, rationale and justification for microbiological monitoring programme. Staff training and competence. Maintenance and care of the animals. Husbandry facilities, procedures, specification, transport barriers to isolation facilities.

Doc Refs

Source animal location, lineage data, specification requirements of pig from herd to isolation, prerequisite screening requirements, age, functional organ test programme, isolation QPF facilities structure, welfare, feeding practices, health records, vaccination programme, rationale and justification for microbiological monitoring programme, access, protective clothing, and contact by personnel. Staff training and competence.

Doc Refs

Collection of material site/location of, details of surgical procedure, prerequisite tests and conditions, preservation and/or storage media, protection measures to maintain condition and viability, transport arrangements to site for human implantation or the processing of specialised cells for other manufacturing operations. Procedures for post mortem examination, animal identification, storage of tissues and disposal of the carcass.

Doc Refs

Infection Surveillance (2)

Procedures and practices for the ongoing systematic collection, analysis and interpretation of outcome-specific data, and its integration for the timely dissemination to those responsible for control and prevention. Current and projected impact of disease, identifying methods of control, data requirements for control and prevention, data sources and methods of capture. Roles and responsibilities of key personnel. Routine screening and testing programmes for patients, source animals and archived samples. Systems for data analyses and information dissemination, with practices for confidentiality and access. The investigation and response to a reported incident.

Doc Refs

Notes

(1) *Information on the trial protocol has been developed from the* EEC Note for Guidance for Good Clinical Practice for Trials on Medicinal Products in the European Community, *CPMP Working Party*, January 1991.

(2) *Applicants are advised to consult two reports by the UKXIRA Steering Groups*

a) Report of the infection surveillance steering group of the UKXIRA.

b) Report of the biosecurity steering group of the UKXIRA

Annex Five: Meeting dates

Meetings covered by this report:

5 October 1999

6 December 1999

13 March 2000

5 June 2000

12 September 2000

Dates for future meetings:

4 December 2000

7 February 2001

14 May 2001

10 September 2001

4 December 2001

Annex Six: Publications and references

Copies of the following can be obtained from:

Department of Health, PO Box 777, London SE1 6XH
Fax: 01623 724 524
E mail: doh@prologistics.co.uk

or from the UKXIRA website: www.doh.gov.uk/ukxira.htm

Guidance on making proposals to conduct xenotransplantation on human subjects.
UKXIRA 1998.

Report of the workshop on porcine endogenous retroviruses, 6 August 1998.
UKXIRA 1998.

First Annual Report, May 1997–August 1998.
UKXIRA 1998.

Second Annual Report, September 1998–August 1999.
UKXIRA 1999.

Copies of the following will be available in due course from:

UKXIRA Secretariat
Department of Health
Room 420
Wellington House
133-155 Waterloo Road
London
SE1 8UG

or from the UKXIRA website: www.doh.gov.uk/ukxira.htm

Report of the Infection Surveillance Steering Group: further guidance on infection surveillance aspects of xenotransplantation
UKXIRA 2000

Report of the Biosecurity Steering Group: Guidance Notes on Biosecurity Considerations in Relation to Xenotransplantation
UKXIRA 2000

Annex Seven: Contact points

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