World Health Organization

Xenotransplantation Advisory Consultation

Geneva, 18-20 April 2005

Meeting Report

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Introductory Note from the Secretariat

This report summarizes the issues discussed and the conclusions reached at a meeting held at WHO Headquarters in Geneva from 18 to 20 April 2005. The meeting was arranged in response to the World Health Assembly Resolution (WHA57.18) on Human organ and tissue transplantation adopted in May 2004. Section II of the Resolution concerned xenotransplantation and specifically requested the Director-General of WHO to take further action to:

- improve communication and collaboration among health authorities in Member States;
- collect data on xenotransplantation practices;
- inform members of any xenogeneic infectious events;
- provide technical support in the field to Member States, and
- report back to the Assembly.

The meeting was organized by the Clinical Procedures Unit in the Department of Essential Health Technologies and brought together 14 recognized experts in a variety of aspects of xenotransplantation from around the world and WHO staff. The purpose of the consultation exercise was to bring WHO up to date with the current position of xenotransplantation and any likely developments. In the light of any developments and the WHA Resolution, to consider the relevance of existing WHO guidance and to decide what, if any, further action is required by WHO to fulfil the requirements of the Resolution.

The report represents the views of the participants. It was circulated to all participants to allow them to comment on the report and in particularly on the Recommendations.

We owe a special debt to the Chair of the meeting, Dr Carl-Gustav Groth, for his skilful steering of the group through some difficult and complicated issues and on guiding them to soundly based conclusions on further action which WHO should take in the field. We are also grateful to Dr Peter Doyle for his preparation of the report.

MEETING REPORT

Opening Session

Dr Steffen Groth, Director of the WHO Department of Essential Health Technologies (HTP/EHT), welcomed the participants to the meeting. He explained that WHO interest in xenotransplantation had increased following discussions of access to transplantation and its safety and ethics during the 112th meeting of WHO's Executive Board in May 2003. The World Health Assembly (WHA) formalized its approach in Resolution WHA57.18, adopted in May 2004.

It was important to remember that WHO had already been active in the field of xenotransplantation. Guidance had been provided on Infectious Disease Prevention and Control (WHO/EMC/ZOO/98.1). A Summary of the joint WHO/OECD "Consultation on xenotransplantation Surveillance" had been published (WHO/CDS/CSR/EPH/2001.1) as had WHO's "Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation and Coordination". The EHT Clinical Procedures (CPR) unit, which is in charge of transplantation, is cooperating with other relevant WHO departments, particularly those responsible for communicable disease surveillance and response.

WHO recognized that xenotransplantation could bridge the gap between demand for and supply of human organs for transplantation and lead to the development of other new technologies such as medical devices and stem cell technologies. Reports of recent experiments were encouraging but concerns remained about the potential threat to public health of novel infections arising from xenotransplantation. This was of particular concern because of the lack of regulation of xenotransplantation in some countries. It was true that some countries had developed good regulatory systems and others had imposed a moratorium on xenotransplantation, but there is no homogeneous approach to regulation. The WHA recognized the need for a global approach to xenotransplantation. Resolution WHA57.18 put the responsibility for control of xenotransplantation on Member States and their national health authorities (NHAs). However, it also required WHO to assist Member States and the purpose of this Consultation was to develop a WHO plan of action. Dr Groth reminded participants that there was an important balance to be struck between the risks and the benefits and WHO would not wish the participants to overemphasize the former at the expense of the latter.

The participants were then formally introduced and Dr Carl-Gustav Groth was elected to Chair the meeting. Dr Peter Doyle was appointed as Rapporteur, supported by Dr Léo Bühler from the Hôspitaux Universitaires Genève.

Session 1 – Introduction and objectives of the consultation

Dr Luc Noël (Coordinator, CPR) explained that the aim is to achieve clear outcomes in the form of work to be undertaken by WHO based on the requirements imposed on the Director-General by Resolution WHA57.18. The plan for this first session was to explain how WHO worked and to revisit the WHO xenotransplantation documents to determine their current relevance. In the second session, participants would be asked to present their current understanding of developments in xenotransplantation and any concerns they may have. The remainder of the meeting would be focused on identifying actions that WHO could take, within its remit, to foster a global approach of issues in

xenotransplantation. He hoped the meeting would identify things that WHO could deliver with realistic and achievable outcomes.

WHO and xenotransplantation – Dr Luc Noël

Dr Noël reminded participants of WHO's mandate and resources. He described WHO's activities in relation to transplantation. The WHA had published "Guiding Principles in Human Organ Transplantation" (WHA44/1991/REC/1, Annex 6) in 1991 on the ethics of allogeneic organ and tissue transplantation. Following the request of the 112th Executive Board, a global consultation process was organized which culminated in a meeting held in Madrid in October 2003 on "Ethics, access and safety in tissue and organ transplantation: Issues of global concern". Following the Executive Board's request these issues also included xenotransplantation. The report lead to the adoption of Resolution WHA57.18. The Resolution urges Member States to ensure national oversight of procurement, processing and transplantation of cells, tissues and organs and to ensure accountability and traceability: also to work to ensure harmonization of practices, to set up an ethics commission, to extend the use of living donors and to protect the poor and vulnerable. It requested the Director-General to update the Guiding Principles, promote international cooperation, increase access for citizens and assist Members States in combating organ trafficking.

The second half of the resolution deals with xenogeneic transplantation. It urged Member States to allow xenotransplantation only if there is proper regulatory oversight and surveillance in place; to work to harmonize global practices, including protective measures to reduce the risk of infectious disease events, and to support international collaboration. It requested the Director-General:

1. To facilitate communication and international collaboration among health authorities in Member States on issues relating to xenogeneic transplantation;

2. To collect data globally for the evaluation of practices in xenogeneic transplantation;

3. To inform proactively Member States of infectious events of xenogeneic origin arising from xenogeneic transplantation;

4. To provide, in response to requests from Member States, technical support in strengthening capacity and expertise in the field of xenogeneic transplantation, including policy making and oversight by regulatory authorities;

5. To report at an appropriate time to the World Health Assembly, through the Executive Board, on the implementation of this Resolution

Work had already started to meet the requirements of the Resolution but resources are limited. The first objective is to recruit NHAs through a process of regionally based global consultation. The Asia region had been identified as a priority because of unmet needs and Latin America would be next. Europe is already well developed largely because of work of the Council of Europe (CoE) and more recently the adoption of the European

Union (EU) Tissues and Cells Directive[1]. WHO has planned meetings for representatives of NHAs in charge of transplantation of the following three WHO Regions in November 2005: South East Asia, Eastern Mediterranean and Western Pacific. The intention was to recruit all NHAs by the end of the year and combine them with other stakeholders such as transplant organizations, patient groups and professional societies into a Global Forum on Transplantation by 2008.

The second WHO aim is the development of a global transplant knowledge base. This will be based on information obtained from the network of NHAs and collaboration with scientific and professional societies.

The four 'pillars' of the knowledge base would be:

- activities and practices;
- legal frameworks and organizational structures;
- adverse event risks, threats and safety measures; and
- xenotransplantation.

There is a need for transparency and easy access to the information in the database.

The third aim is to work to increase access to transplants in Member States, with renal and corneal transplantation as the priority. WHO participated in the Amsterdam meeting on live kidney donors and supports the Amsterdam consensus statement[2]. In the field of human cell- and tissue-based products for transplantation, WHO organized a first global consultation on regulatory guidance in Ottawa with the support of Canada

In the case of xenotransplantation the knowledge base should be a resource for Member States and for the global xenotransplantation community. The definition of xenotransplantation adopted by the WHA in Resolution WHA57.18, and therefore supported by 192 countries, is consistent with those adopted by the USA and the Council of Europe. The definition does not cover non-living material but does now include procedures in which there is *ex vivo* contact with animal cells. An example is the culture of human keratonicytes for the treatment of burns, using a feeder layer of mouse cells, which has had widespread global application for up to 20 years. Different xenogeneic practices carry different risks but risk assessment depends on adequate information and documentation.

Currently xenotransplantation research is principally confined to animal-to-animal models. However, there are concerns about the possibility of human trials in poorly regulated countries and the use of living animal material in 'quack' treatments and some 'traditional' medicines. There is great heterogeneity in the animals reported to be used including pig, goat, shark, rabbit and sheep. Similarly the material used might come from embryos, foetuses, young or adult animals. Animals may be native or genetically modified and there might or might not be proper animal husbandry. With such a variety of practices there were clear risks relating to immune reactions including rejection, inadequate or inappropriate function and the passage of known infections and the development of novel

[1] Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.

[2] The Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor, Transplantation: 78; No. 4, 27 August 2004

infections. There was a risk not just to the recipient but to his/her close contacts and to the wider population. For example, there is a long list of pig viruses most of which can be eliminated by breeding and the use of closed herds, except possibly retroviruses, but this can only be achieved by consistently applying stringent standards. Recent publications indicated that clinical trials of a genetically modified pig heart were likely before long. This added urgency to the need to gather information about current practices, agree on a strategy to further the WHA Resolution and prioritize WHO activities in the field.

Discussion

One option was to try to impose a moratorium on xenotransplantation unless there is an effective regulatory structure in place. This may give rise to concerns in the field as it could slow down development by preventing research. On the other hand, it could set a good example to less well-developed countries. Countries known to have imposed a moratorium include India, Canada, Australia and the Netherlands. In the case of Australia and Canada it was imposed because they did not, and still do not, have a system in place for national regulation or surveillance. One aspect of xenotransplantation, which has received little attention, is the risk to the animal population of novel or modified animal diseases, particularly arising from the genetic modification of animals. There is a risk of developing highly contagious animal diseases which, if there is poor containment or an accident, could spread rapidly to the animal population.

Review of WHO xenotransplantation documents – Dr Eda Bloom

Dr Bloom explained that this was her personal view of the documents reviewed and not the view of the US Government. However, her comments had been approved by the Center for Biologics, Evaluation and Research at the FDA. There are three relevant documents.

Xenotransplantation: Guidance on Infectious Disease Surveillance (WHO/EMC/ZOO/98.1)

It was valuable for WHO to have a public, scientifically-based document summarizing the risks posed by xenotransplantation. The guidance had the merit of brevity although it did cover adequately the potential disease risks posed by xenotransplantation, including the risk of unknown agents, and measures that could be taken to reduce the risks. It considered methods of protecting the recipient and an evaluation of infectious disease management strategies. However, it needed updating and would benefit from having relevant citations included in the text and appropriate references to be included. It was suggested that more emphasis be placed on issues involving infectious disease control measures at the levels of recipient and intimate contacts. The document would probably be better framed as 'recommendation' rather than 'requirement' and consideration might be given to using the CoE format of a recommendation with an accompanying detailed explanatory report. A list of more detailed suggestions for updating specific parts of the document was presented for consideration.

OECD/WHO Consultation on Xenotransplantation Surveillance: Summary (WHO/OECD/CSR/EPH/2001.1)

The Report is a summary of a consultation on xenotransplantation surveillance which included a range of experts such as epidemiologists, infectious disease experts and

representatives of industry and governments. The discussion focused on what would be needed in an international surveillance system and much of it is still relevant. It defined the objectives of a surveillance system, the need for countries practicing xenotransplantation to have such a system and a means of rapid international exchange of information about risks and events. It recommended that xenotransplantation surveillance builds on existing resources and that the network should be 'owned' by all participants. However, it was recognized that xenotransplantation surveillance will need to develop new paradigms to detect unknown agents and that testing should be standardized and able to take into account the effects of immunosuppression. Although international consensus has been reached since the meeting on a definition of xenotransplantation, international consensus is still needed in other areas such as what constitutes a xenogeneic infectious event, particularly given the need to differentiate between an infection and disease.

WHO Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation and Coordination (WHO/CDS/CSR/EPH/2001.2)

The objective of the document is to provide a framework for the development of an international xenogeneic infection/disease event surveillance network to ensure that there would be effective detection, reporting and response to any such event. International surveillance should be harmonized, cooperative and coordinated. To that end the document proposes case definitions related to possible or probable xenogeneic infections and syndromes. The document advises on the collection of relevant data including biological samples, the establishment of databases and registries and the information which the system should produce in order to ensure an appropriate and effective response. The document suggests a minimum dataset and proposes the development of an international surveillance network which would link the local xenotransplantation activity and recipients to intermediate, national and international organizations, whilst at the same time preserving patient confidentiality. The proposed roles and responsibilities of each level were described and suggestions made for other partners in the network. The accompanying annexes included a glossary, potential sources of xenogeneic infection and examples of reporting forms. In commenting Dr Bloom thought there was much value in the document but the question was where to go now. She suggested that any surveillance system needed to be simple with national authorities free to collect data in its own way. The essential aspect is for a national system to collect adequate information on xenotransplantation activities and pass on minimum data summarizing the number and type of xenotransplant-tation activities and any adverse events detected. As long as there is proper linkage, further data could be obtained from the local level if required. She suggested that to this end there should normally be no real need for communication from the local level direct to the international level as long as national surveillance was well developed. In some Member States, at least initially, it might be essential for units performing xenotransplantation to communicate directly with an international level. The key to further progress was WHO leadership.

Discussion

Dr Bloom was thanked for a very helpful review and her suggestions for updating the document. One omission from the documents was explicit information about xenotransplantation practices. It should be established just how little xenotransplantation is being performed. Most activity is still in the research field. However, NHAs needed to be aware of commercial activities which included acceptable forms of xenotransplantation

such as skin cell culture (which should however be regulated) and high risk procedures such as 'rejuvenation' using injected animal cells. Member States needed to know what activities to look for and advised what types to allow and what should not be performed. It was not clear whether the documents were generally intended to encourage or deter xenotransplantation. The ideal was to encourage responsible xenotransplantation and deter the rest. The definitions used should be revisited. In general infection disease surveillance infections are defined as 'suspected', 'probable' or 'confirmed'.

It was agreed that the technical documents should be updated but possibly reformatted to make all the key material accessible. It would be important to provide descriptions and definitions of various xenotransplantation practices to help Member States identify xenotransplantation activities in their area. The updated documents should give more detail on the regulation of xenotransplantation and the steps required to maximize safety and quality such as the use of closed colonies, etc. The document(s) should also contain advice on contingency plans to cope with any adverse event and the need to keep proper samples from both source animals and recipients. Above all, the document(s) must establish clearly what is and what is not acceptable in the field of transplantation.

Session 2 – Presentations by participants

Drs Kanda and Hirota – Japan

Regulation of xenotransplantation in Japan is based on Public Health Guidelines published in 2002, not on a law. The Guidelines provide a definition of xenotransplantation consistent with that adopted by the WHA. They include a system for reviewing xenotransplantation protocols, how to obtain informed consent, quality controls for donor animals, the records and samples to be kept for donor animals and recipients, lifelong recipient surveillance and a reporting system. However, several problems had been identified. Would it be possible to keep records and samples for the required 50 years? Could asymptomatic patients be forced to comply with lifelong surveillance? What to do about patients receiving xenotransplants in countries without proper regulation? How can unknown or novel pathogens be detected? In terms of xenotransplantation activity, it was known that some 500 patients had been treated with skin cultured using 3T3 feeder cells since 1985 and more recently corneas had been successfully repaired. Although mouse cells can sometimes be detected in the skin, no pathogens had been detected therefore new, more relaxed guidelines covering such cell culture techniques were published in 2004. Meanwhile on the research front some Japanese Companies are developing genetically modified pigs. The modification involves the introduction of human DAF (CD55) plus human GnT-III (reduces GAL on cell surface) and knockout of alpha-Galactosyltransferase. No clinical trials were planned to date. There are no other xenotransplantation activities in Japan. At least one company is trying to establish a commercial skin grafting facility but the outcome is not yet clear.

Dr Jung – Korea

Xenotransplantation is a very important issue in Korea. There are nearly 7,000 people waiting for an organ transplant and almost as many needing a tissue transplant. The Government is therefore investing heavily in three programmes, xenotransplantation, cell technology and stem cells therapies. Research is aimed at overcoming the recognized problems of rejection, function and infection but there is also work to be done on the ethical, legal and social implications of such techniques. The Government is preparing a law to cover xenotransplantation and is funding research. Two techniques for genetic

modification are being pursued: the first uses a combination of genetic insertion and knockout, the other cloning technology. One team has almost overcome hyperacute rejection and believes the infection risk is low. It is possible that there will be a clinical trial as early as possible. There is evidence from surveys of public support for xenotransplantation. Nearly 40% of people know what it is and some 60% believe it will prove useful to society. Currently there are no provisions to regulate xenotransplantation specifically but the Bioethics and Biosafety Act could be used to control some aspects, particularly cloning techniques. Draft Ethical Guidelines for xenotransplantation are in preparation covering an institutional review board, somatic nuclear transfer, animal welfare, transgenic animals, biosafety, clinical trials, follow up of patients, data collection and storage and these are likely to be translated into law. Trials are about to start using aseptic non-human primates.

Dr Qi – China

There is no regulation of xenotransplantation in China at present. The Ministry of Health is drafting regulations. The main concerns are efficacy, ethics, and the risk of transmitting infection. The Ministry recently conducted an investigation to get a complete picture of what is happening in China. It revealed that chemically treated pig skin has been used for the treatment of burns. Trials of pig pancreas islet cells have been stopped for lack of any good results. Three hospitals in Beijing use bovine jugular vein for the repair of congenital right heart defects. The longest survivor had reached 18 months. Bovine pericardium has also been used to dress the surface of the liver in liver transplants.. The investigation had covered both civilian and military hospitals.

Dr Ichhpujani - India

It is important to understand the situation in India. The WHO South East Asia Region covers 11 countries with a population of 1.5 billion of whom some 600 million live on less than US$1 per day. There are undocumented, large cross-border flows and many people from the region go to India for treatment. Transplantation is regulated by the Transplantation of Human Organs Act (THOA) enacted in 1994. This sets out a framework for regulation of the removal, storage and transplantation of human organs. It also allows for an appropriate (state) authority to inspect and, if satisfied, accredit a unit for performing transplantation procedures. The Act forbids any commercial dealings in organs. The Act covers brain death to allow cadaveric donation. Living organ donation is restricted to close relatives or others less closely related only if specifically approved. A THOA Review Committee has been constituted which is now finalizing the guidelines for authorization committees, etc. India has an Organ Retrieval and Banking Organisation (ORBO) to coordinate cadaveric donation. The Act has been in place for some 10 years but donation rates have gone down. India currently has a moratorium on xenotransplantation and experts consulted prefer to improve allogenic transplantation rather than develop xenotransplant-tation. Many are concerned about the recognized risks of xenotransplantation. In addition there are country-specific concerns which include the risk of the development of xenotransplantation tourism, the difficulty of enforcing regulation, restricting xenotrans-plantation to a few centres, religious and animal welfare concerns, the difficulty of testing for known and unknown pathogens and ensuring prolonged recipient follow-up. The xenotransplantation involves many ethical issues and India would be firming up guidelines to permit it once the success of xenotransplantation is established scientifically and is considered a better alternative to human-to-human transplantation. Until such time it would be considered experimental only. There is a view that xenotransplantation could be permitted if/when a proper regulatory system is in place but others prefer to see

developments in other countries and only adopt them when successful. India, however, as per international requirement, is willing to cooperate for xenogeneic infection/disease surveillance. There had been a rumour about goats being bred for xenotransplantation in India but it has not been substantiated.

Dr Khan – South Africa

Most of the continent of Africa has very little transplantation activity. What there is, is concentrated in North Africa where there are living related kidney programmes in line with the practice in other Middle Eastern countries. South Africa has a small but well organized programme regulated by the Human Tissue Act. There is no regulation covering xenotransplantation. The programme initiated by Dr Christian Barnard used 'piggy back' baboon hearts. Pig skin has been used for the treatment of burns and about five well documented liver support procedures have been performed. There has been a programme of research on transgenic pigs imported from Australia in which organs were transplanted into apes but the use of baboons for research is strictly controlled. The facilities for dialysis are limited so xenotransplantation would fill a very real need. It is hoped that guidelines for xenotransplantation will be developed for the future.

Prof. Valdes – Mexico

A xenotransplantation project was started in Mexico in 2000. The reason was the very high prevalence of diabetes. Some 12.8% of the population have diabetes of which 10% are Type 1. On average, people with diabetic complications occupy 45% of hospital beds. Even with the development of intensive conventional treatment there are complications and the chances of allotransplantation are limited by the availability of donor organs, whether for whole body or islet cell transplants. The challenges of xenotransplantation are well recognized. They minimize the risk of transmitting infection, ensuring adequate function and the survival of grafted cells. The question was whether an immunologically-privileged site could be created. The initial project involved 12 adolescents with Type 1 diabetes. The technique involved the implantation of four stainless steel mesh cylinders in the lower abdomen which became embedded in autologous collagen. After two months the cylinders were exposed, an occluding plug removed and the cavity filled with a mixture of 7-day-old pig islet cells mixed with Sertoli cells. No immunosuppression was used. The results after one year showed that, of the 12 subjects, six had no response but the other six showed decreases in exogenous insulin requirements and two remained insulin independent for several months. After 3-5 years one of the devices was removed and new ones implanted in an attempt to achieve insulin independence. Tests on the material removed from the devices showed viable islet and Sertoli cells. There was no detectable impact on the subjects' immune systems. Altogether an interesting result. It had to be recognized that the subjects were adolescents and so officially children when they gave their consent. However, the trial was authorized by hospital, university and national authorities. Xenotransplantation is regulated by 1999 National Health Law and is regularly reviewed by a national Committee. There have been reports of unauthorized and questionable xenotransplantation practices in Mexico such as the use of shark cells to try to repair spinal chord injuries and advertisements for the transplantation of pig pituitary cells. The Ministry of Health investigates any such reports and other forms of alternative medicine.

Dr Tönjes – The Position in Europe

This first presentation was given on behalf of the European Medicines Evaluation Agency (EMEA). There are two important EU documents relevant to the regulation of xenotransplantation. Annex 1 of Directive 2003/63/EC covers the testing of medicinal

products and covers somatic cell therapies of human or xenogeneic origin. Directive 2001/20/EC, the Good Clinical Practice Directive, became a requirement in all Member States in May 2004. It requires Member States to adopt good clinical practice in trials of medicinal products. Trials will need authorization and trials of somatic cell therapies have a firm timetable for authorization. These time limits do not apply to xenotransplantation trials. The Council of Europe has produced a Report on the State of Xenotransplantation and an important Recommendation (Rec. (2003)10)) requiring Member States to ensure that no xenotransplantation takes place without regulation. It made the point that "considering that xenotransplantation of cells and tissues is already being carried out in some States, stringent regulations are thus urgently required". The Committee for Proprietary Medicinal Products (CPMP) of the EMEA has also produced a brief but comprehensive document "Points to Consider on Xenogeneic Cell Therapy Medicinal Products". Missing from the document was detailed safety standards, the training of staff involved and air quality but it is only an advisory document and currently there are no trials ongoing. In the face of this regulation it was hard to understand why a company in Kiel was allowed to advertise the injection of rabbit cells to 'cure' a variety of conditions. However, in Germany it is for the Bundesland to act against such organizations and it appears that the local Medical Association has defended the practice on the grounds of clinical freedom!

Dr Tönjes – Germany

Xenogeneic research is one of four Sections in the Division of Medical Biotechnology in the Paul-Ehrlich-Institute. A great deal of research has gone into the infectious risks of xenotransplantation, particularly into porcine endogenous retroviruses (PERVs) as these are seen as a major risk. The presence of PERVs varies between types of pig. Some strains of the miniature pig appear to be PERV-free, at least for known infectious PERVs. Peccaries are also negative for PERV gene sequences. Evolutionary analysis shows that of the three types PERV-A is the oldest, probably 7,500,000 years old, and PERV-C the youngest. There appears to be an east/west gradient with western varieties of pig being the least likely to carry PERVs. This opened the way to breeding PERV-free pigs, a major advance in xenotransplantation. Meanwhile, there remains a very long waiting list for organ transplants in Germany and 25% of those on the list die while waiting for an organ. The German Association of Physicians produced a Position Paper on Xenotransplantation in 1999. It concluded that the level of risk was such that xenotransplantation should not be performed. The Association did, however, continue to prepare a guideline but work on it was stopped in 2004. German Drug Law (2004) classifies xenogeneic cell based products as medicinal products and the Paul-Ehrlich-Institute is the Competent Authority for regulating such products. A moratorium on xenotransplantation is being considered but to date no law has been published. It is accepted that moratoriums can be counter productive as industry may back out of research thus slowing progress whilst at the same time completely unregulated practices are allowed to continue.

Dr Bühler – Switzerland

Switzerland remains near the bottom of the European organ donor league with only 70-80 donors per year and some 400 organ transplants. So far clinical experience of xenotransplantation is confined to a trial of intrathecal transplants of encapsulated modified hamster kidney cells implanted in the spinal cord of patients with amyotrophic lateral sclerosis. The cells produced a neurotrophic factor but showed no clinical benefit. Four groups are undertaking basic xenogeneic research with support from the Swiss National Research Fund. Clinics in Switzerland were offering "rejuvenating therapy" using

injected lamb cells but this was stopped by a new transplantation law proposed in 1999 which came into force in 2001. Xenotransplantation is allowed with federal authorization following modification of the Transplantation Law in 2004. It now includes six articles regulating xenotransplantation. The law requires xenotransplantation to be authorized by the Federal Authority, follow up of recipients, testing of donor animals and human recipients and a national register. However, the Swiss authorities would still be grateful for further WHO advice as it is considered likely that there will be trials of new cell therapies in the near future. International collaboration is required to establish guidelines to allow safe and ethical xenotransplantation. It was thought that WHO and the International Xenotransplantation Association (IXA) could cooperate on preparing such guidelines and possibly establishing a registry.

Dr Doyle – UK

The position in the UK is well documented. Following headlines about xenotransplantation in 1994, the Government moved quickly to set up an expert group which produced the Kennedy Report which, in turn, recommended that a regulatory body be established. The UK Xenotransplantation Interim Regulatory Authority (UKXIRA) first met in May 1997. The UKXIRA and xenotransplantation regulation in the UK is not based on a specific law but on an order from the Secretaries of State for Health that no xenotransplantation can take place without their express authorization. Such authorization would only be given if the UKXIRA is satisfied that the trial/procedure is an acceptable risk and any other requirements have been met. The UKXIRA has a formal application process and produced detailed guidance to applicants. It has also produced reports on animal husbandry, physiology and infection risks, all of which are available from its website (www.advisorybodies.doh.gov.uk/ukxira/index.htm). Over the years there have been only three enquiries about possible trials, one was from Immutran, one from a firm developing an artificial liver and the other a group preparing rat cells for implantation in the brain. The only initial partial application was submitted by the firm developing the liver but did not progress as the firm went out of business. The change of definition adopted by the USA, Council of Europe and WHO posed problems as units using well established skin cell culture techniques involving 3T3 mouse feeder cells required a simpler mechanism for regulation compared to clinical trials. A national mouse cell bank has been set up at NIBSC and, to ensure proper quality, control cell culture laboratories are now inspected and accredited in accordance with the UK Code of Practice on Tissue Banking and, after April 2006, by requirements of the EU Tissues and Cells Directive.

Dr Doyle – Council of Europe

Following from the UK experience, the Council's Expert Transplant Committee (SP-CTO) prepared a short but comprehensive Recommendation (R(97)15) for the regulation of xenotransplantation which was adopted by the Committee of Ministers. It recommended that Member States establish a mechanism to regulate xenotransplantation but did not go quite as far as proposing no xenotransplantation without regulation. In 1999 the Parliamentary Assembly proposed a legally binding moratorium on xenotransplantation in all Member States, and asked the Council to work towards a worldwide moratorium. It asked the two key health steering committees (CDSP and CDBI) to develop a strategy for achieving its aims. In response the CDSP and CDBI prepared a 'State of the Art Report' on xenotransplantation published in draft in 2001 with the final version published early in 2003. Essentially, the Report stated that xenotransplantation had great potential and the risks to both recipients and the wider public could be minimized by careful regulation. On the basis of this report a new more detailed Recommendation (R(2003)10) was adopted in June 2003. The Recommendation included a definition of xenotransplantation consistent

with that adopted by the USA and stated quite clearly that there should be no xenotransplantation without effective regulation. The Recommendation included Articles on the criteria to be met for clinical research and procedures, health protection and animal welfare. It had an accompanying helpful Explanatory Report. However, it is only a recommendation and not binding on Member States.

Dr Giulivi – Canada

The Public Health Act of 1996 allows the Ministry of Health to issue regulations if there is perceived to be a public danger. Following the blood scandal the Ministry issued a set of new much stricter regulations, first for blood and more recently for organs and tissues. A difficult situation arose in 1998 because Health Canada imported transgenic pigs for research purposes but the story in the papers was that they were to be used for transplants. This and other situations lead to the issue of a moratorium on xenotransplantation. In 2003 the Government adopted the Council of Europe Recommendation and will now act to regulate organs and tissues. The problem is collecting the required data and they are going to see if they can adapt the system that works for blood. The idea is to develop tools that make it easy for the clinicians to collect the patient based data they need with infectious disease control as a small subset of the data. A new surveillance system is now being piloted and it is likely that the moratorium will be lifted in the autumn. There was interest in xenotransplantation in some groups, e.g. Edmonton. However, Health Canada has no authority to proactively inspect and accredit tissue banks. Recent problems have been identified with an ear bone bank and live bone donors not being properly tested. It was also recognized that the surveillance requirements should be proportional to the risk

Dr Sykes – USA and IXA

Dr Sykes is President-Elect of the International Xenotransplantation Association (IXA). Transplant waiting lists are only the tip of the iceberg representing only a small proportion of those who could benefit from a transplant. Xenotransplantation offers a potentially unlimited supply of high quality, short ischaemic time, elective transplant procedures. There is also potential for genetic engineering and tolerance induction and xenogeneic cells may also be resistant to some common human pathogens. The potential scope for xenotransplantation is wide, covering islet cells, neural cells, kidneys, hearts (mostly heterotopic), livers and short-term bridging procedures. However, after early enthusiasm the risk of PERV transmission led to public suspicion and withdrawal from the field by industry. Recent research showing that not all pigs have transmissible PERVs, and developments with GAL knockout pigs, are both encouraging and have produced renewed interest. The IXA wishes to encourage xenotransplantation and has produced position papers covering concerns about xenotourism, the need for international harmonization of guidelines, the promotion of high standards by IXA members and that there should be a high expectation of benefit before trials commence. These standards have to be met by papers published in Xenotransplantation. Recent non-human primate research using GAL knockout miniature pigs showed 50-179 day survival in heart transplants. Pig thymic transplants have also been used to induce tolerance as a basis for renal transplants. An animal survived for 83 days with a functioning pig kidney which showed no evidence of rejection at the time of the animal's death. The animal received a pig thymic transplant with the kidney and no steroids were used. Such results are encouraging but clinical trials are still a few years' away.

Dr Bloom – US FDA

In 1993 the FDA announced that its Current Statutory Authorities applied to somatic cell therapies. However, it became clear that xenotransplantation was different and

needed new guidelines. A Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation was first published in 1996 and in final form in 2001. The US Food and Drug Administration (FDA) is the regulatory agency. The trial sponsor is responsible for all aspects of safety. There is no specific xenotransplantation regulation but FDA can use its current regulations, particularly those that pertain to safety considerations, to place clinical holds on investigational clinical work. Such clinical holds can be placed before initiation of a trial, or after a trial has already started, based on available evidence. There is ongoing collaboration between US Public Health Services Agencies. The Secretary's Advisory Committee on Xenotransplantation (SACX) discusses issues broader than FDA purview, which covers safety and effectiveness, as it also covers ethical, economic and legal aspects. Its draft reports went on line in 2005. Another initiative is the establishment of a National Xenotransplantation Database (NXD). It is currently under development and will contain seven categories of information. To date the FDA has produced three guidance documents for industry covering public health issues, precautionary measures and source animals. The last of these is consistent with the PHS guideline but goes further in providing specific advice regarding source animals, manufacturing, product testing, current good manufacturing practices, preclinical studies and clinical trial design issues as they pertain to xenotransplantation. Over the years there have been 40 Investigational New Drug Applications (INDs) covering all forms of xenotransplantation and using material from a variety of source animals, e.g. mouse, pig, fruit fly, cow and non-human primates (NHP). Altogether some 470 patients have been treated under the INDs but not every IND resulted in the treatment of patients.

Session 3 – Oversight and guidance

Introduction

This was the first of four working sessions aimed at deciding how best WHO could fulfil its responsibilities as set out in the WHA Resolution. Any initiatives proposed needed to be pragmatic and have outcomes that are deliverable. It is important that WHO is able to recruit the cooperation of NHAs, which will be responsible for implementing effective regulatory control of xenotransplantation and establishing effective surveillance for public health risks. The first item for consideration will be how to get an effective message to NHAs and what to do about existing WHO guidance.

Advocacy and guidance material for Member States

There was unanimous agreement that xenotransplantation should not take place without a regulatory mechanism in place overseen by NHAs. The problem is that there is a wide range of xenotransplantation practices, some of which may not be recognized by NHAs as xenotransplantation. In addition, different xenotransplantation practices posed different risks and may require varying levels of regulation. For example, there are current practices which appear safe like skin culture for burns, etc. New initiatives in the form of clinical trials might involve standard or genetically modified animal organs, tissues or cells derived from embryos, foetuses, infants or adult animals. Standard animals may carry a different risk from a genetically modified animal, as might implantation of the organ, tissue or cells compared to *ex vivo* perfusion. Short-term bridging may be safer than permanent implantation. Finally, there are a number of 'commercial' practices of a dubious nature such as the injection of shark or rabbit foetal cells intended to 'cure' degenerative diseases or secure 'rejuvenation'. Although xenotransplantation poses three important risks, for WHO it is the infectious risk which is most important. The fact that there are ongoing xenotransplantation trials makes the introduction of effective regulation more urgent.

In view of the variety of practices and risks, it was agreed that the first section of any new guidance should describe existing practices to illustrate what practices NHAs need to identify as a precursor to deciding what to do about them. In setting the scene, it would also be helpful to stress the potential benefits of well conducted research and trials contrasted with the high risks of badly controlled practices. It is essential not to prevent well regulated research, as there is still much more work needed before the potential benefits of xenotransplantation can be realized.

Once NHAs have identified xenotransplantation practices, the potential risks should be assessed. If a practice is uncontrolled and unjustified by research, the practice should be prohibited. If the risk is assessed to be acceptable to the individual and community, then the regulatory system should work with those involved to minimize the risks and maximize safety and efficacy. There should be proportionality between the assessed risks and the level of regulation. The potential risk to the public and animal populations remains the highest priority. That said, it should be noted that the infectious disease risk is now considered to be lower than anticipated two to three years ago. Conditions of good animal husbandry and proper regulation can reduce infection in animals and PERV transmission is now thought to be less of a problem. There must be regulation and surveillance of xenotransplantation and the case should be set out in simple guidance to all NHAs.

The form in which guidance to NHAs should be developed was discussed. More than one document was needed. A short document would alert NHAs to the problem but many would then need more detailed technical guidance on how to regulate effectively. Documents needed to by practical and easily adapted to the circumstances in individual Member States.

It was agreed that WHO should produce three documents:

- *a 1-2 page statement of the issue for policy makers;*
- *a rather longer, say 5-page, explanatory document introducing a set of tools or annexes; and*
- *a set of detailed tools/annexes dealing with specific topics, e.g. regulatory systems, animal husbandry, safety and efficacy, quality control, surveillance*.

There is no need to start from scratch but to reformulate and update existing WHO guidance. The guidance should make it clear that the higher the risk of any trial, the higher the expected benefit should be. Regulatory bodies should have the expertise to assess the risk of rejection, function and disease transmission before authorizing any trial. *It was agreed that WHO should update its documents as the basis for the proposed tools and that, later in the meeting, at least the substance of the proposed one page document should be agreed, if only as the basis for a press release.*

Role of WHO in information gathering and sharing

Website

WHO does have a transplantation website (www.who.int/transplantation) but currently it gives access to existing WHO documents but not much else. As a start, *it was agreed that the existing documents should be translated into all six official WHO languages.* Further thought should be given to the development of the WHO website to make it a more effective tool for communicating information and guidance about

transplantation and xenotransplantation. Xenotransplantation had its own page but this only gave access to the three guidance d

International database of xenotransplantation practices

The need for and international register of xenotransplantation clinical trials was identified at the Madrid meeting. The question is whether such a register is practicable and if so, how it would work and how information would be obtained. Many companies would not be willing to disclose details of their research to rivals. For example, the FDA has access to the IND database so could provide information on the number and types of trial. However, the law prevents disclosure of details about the investigators. The FDA gets information on xenotransplantation from around the world provided on a voluntary basis and it is incomplete. The IXA does not have a register of trials but could ask members to submit details to a database. An international registry could also have a role as an educational tool by seeking information on, e.g. strain of pigs, type of immunosuppression used, etc.

There are already international transplant registries such as the Islet Transplant Registry held in Guissen in Germany. There are similar registries for liver, heart and other forms of transplantation such as haematopoietic progenitor cell (HPC) transplants. The problem is that such registries are for a specific form of transplantation and the corollary would be several xenotransplantation registries. Researchers would be unlikely to provide details for a single, non-specialist register. Clinicians doing routine skin culture would be unlikely to see the need for registering and it was even more unlikely that those using sheep or other cells for questionable 'treatments' would contribute. Furthermore, WHO really wanted a register principally as a means of identifying potential public health risks.

It was agreed that, initially at least, any register or database needed to be simple. A register should be set up on a country basis and contain details based on some simple questions for NHAs. These would include what xenotransplant practices have been identified, whether they are regulated and, if so, provide details of the regulatory authority. Modern web technology would allow NHAs to update their own entry. This is the way the WHO global database for blood safety was started (albeit it has since had problems). The ideal result would be an international register of xenotransplantation trials held by WHO, plus an inventory of all xenotransplantation practices. As previously noted, such data is not readily available. Transparency is essential so any register or database must be online and accessible by the public.

WHO should seek to establish a xenotransplantation focal point in every NHA which is to be used to assess activity in their country. It was recognized that NHAs may not be willing to participate and particularly to share any problems with the rest of the world. However, the very process of developing contacts in each NHA will help develop local expertise and hopefully lead to increased cooperation. An advantage of getting the more questionable practices into the public domain is that people going for e.g. 'rejuvenation' are made aware that it is a xenotransplantation procedure. Although there is no current evidence that 'fresh cell therapies' are dangerous, there is a concern about transmission of transmissible spongiform encephalopathies (TSEs). Transmission of diseases from animals to humans does happen (e.g. SARS, HIV) so it has to be concluded that there is a real risk that disease transmission
will occur at some time.

It was agreed that:

- *WHO should opt for a country by country inventory of xenotransplant practices seeking information from NHAs.*
- *At the same time the IXA should be asked to do a survey of members.*
- *WHO should establish a restricted access website for NHAs to submit data.*
- *Data should be made available to the public*

In time the data ascertained will grow as regulation improves. Another possibility would be to seek feedback via the website from the public. They could be asked to contact WHO to tell them about any experience they have had of xenotransplantation. The details could then be reported back to the relevant NHA for further investigation if required. *It was agreed that the work might best be performed by an outside collaborating centre such as a university department, national transplant organization (NTO) or professional society*.

In taking forward this work, it is essential to reinforce the message that xenotransplantation has great potential if done well, but could pose a grave threat to public health if done badly, hence the need for effective regulation to ensure safety and efficacy.

Session 4 – Developing expertise and quality

Expert laboratories

There are two essential roles for specialized laboratories in xenotransplantation. The first is to identify reliable animal agents that could be transmitted to humans and to identify their transmission and any resulting pathology. But there is also a need to be able to detect novel agents that might be the cause of a disease outbreak. In xenotransplantation, laboratories are a key resource as they are looking for pathogens which most labs are not equipped to test for, and may also be required to detect previously unknown pathogens. There was also a need for high quality animal testing in the case of an outbreak of disease in the animal population due to a novel pathogen. The question is whether WHO should have a role in ensuring adequate global laboratory competence in the field to ensure high standards of quality assurance and the detection of novel agents. For example, could WHO help improve the performance of laboratories testing for PERVs or other agents by, for example, fostering collaboration between laboratories, developing biological standards, establishing a single reference lab or a quality assurance system?

Currently only 28 countries have VSL 4 laboratories but they do form some sort of network. A big problem facing xenotransplantation is not just the need to test samples but also to store blood and other samples required to ensure the detection of pathogens. This is potentially a big commitment and long term storage is essential. HPC transplantation has already experienced the problem, which needs a lot of funding. However, this issue will need to be addressed by NHAs and regulatory authorities.

There is currently no formal collaboration between xenotransplantation laboratories at present and, because of the relatively low level of recognized xenotransplantation activity since 2001, there has been no pressure to increase collaboration. A lot of work has gone on but only via personal contacts. The FDA held a workshop on PERVs and considered the possibility of developing a 'virtual' collection of agents via an online system. However, there are many other considerations such as laboratory quality standards,

air quality, etc. There are currently no laboratory standards for PERV testing, although standards are being developed. There are already standards in the network for most viruses but not necessarily for all.

It was agreed that, given recent developments, there was a need formalize an expert xenotransplantation laboratory network and ensure that standards are developed for animal agents involved in xenotransplantation.

It was therefore agreed that WHO should:

- *Start by arranging a meeting of relevant laboratories to encourage collaboration, coordinate intelligence about what laboratories can test for on both animals and humans and encourage the development of standards;*
- *Then foster the development of a formal network of laboratories which identifies the capacity of each laboratory to test both animals and humans and establish what standards exist.*
- *Future development may include the production of reference material for biological assays, identification of normative requirements and the involvement of WHO's Expert Committee on Biological Standardization.*

It was important to recognize that WHO could not have a formal role in accrediting xenotransplantation laboratories as such, but should encourage the development of a quality system which can accredit laboratories. It was important to ensure adequate global coverage and cooperation as xenotransplantation disease outbreaks could well occur in a Member State without an expert laboratory and WHO would need to be in a position to mobilize expert help from a recognized network.

Clinical trials

It is important to share expertise in conducting clinical trials of xenotransplantation, accepting that there are confidentiality constraints. Fostering similar standards of practice and passing on lessons to less experienced researchers should reduce risks and increase quality. *It was a greed that WHO should try to bring together those conducting clinical trials, possibility via good practice workshops, probably organized on a regional basis working with NHAs and interested groups*.

Key links

Another means of fostering quality and expertise is networking all those with an interest in the subject. Many organizations held some data relevant to xenotransplantation and linking all the data and making it accessible from any relevant organization would provide a comprehensive knowledge base. Currently WHO has very few formal or informal links. It has a link externally to IXA and internally the Essential Health Technologies section is linked to the Communicable Disease Group.

It was agreed that WHO should:

- *Develop its website to provide links to relevant organizations such as IXA, existing regulatory bodies such as the FDA and UKXIRA and other professional interests;*
- *Work to identify other relevant interests, e.g. associate members of IXA, veterinary organizations, animal welfare organizations, commercial interests.*

Session 5 - Surveillance

It is clear from Resolution WHA57.18 that WHO is expected to disseminate public health alerts arising from xenotransplantation to Member States. In order to alert Member States, such events have to be identified and that is the role of surveillance. Surveillance has been defined as the structured collection of information regarding adverse events and risks requiring a response. *It was agreed that WHO did have an important role in improving xenotransplant risk surveillance.*

In the area of infectious diseases WHO has developed the term "public health event of international concern" and is developing an algorithm for use by Member States to determine when an event should be reported to WHO. If WHO becomes aware of an event via another source, WHO can approach the Member State. Xenotransplantation could give rise to such an event. Once identified, the WHO response is well developed. The source of the problem will be identified and steps taken to break the chain of infection, etc. Putting in a surveillance system is not difficult if the disease is notifiable, but xenotransplantation complications may not be reportable as such. Proper surveillance can form part of a clinical trial but even so it may not be possible to follow all xenotransplantation recipients for 20 years or more. A bigger problem could emerge if/when xenotransplantation becomes routine. Initial responsibility for reporting adverse events should lie with the transplant team but follow up may well go back to a local physician. Local physicians have to be held responsible for reporting to local public health and then back to the transplant unit to close the loop.

It will be up to NHAs to implement a surveillance system as part of their regulatory system but patients and clinical teams need to be aware of the importance of reporting any problems to the local health authority. There will need to be laboratory-based surveillance as well and all events need to be classified as possible, probable and confirmed. NHAs will, as required, report to WHO.

One problem is that there is no system in place for reporting problems in people who have had a xenotransplant and are travelling abroad.

There are many WHO documents that provide guidance on surveillance and both the US PHS Guideline and the FDA Guidance document describe how the surveillance of recipients should be performed by clinical trial sponsors. Surveillance data can be built into the patient follow up as a subset of other routine follow up examination and testing. But the specimens may then be analysed by either the hospital or the public health labs to ensure infection surveillance. Such a system works in Canada. However, xenotransplant surveillance needs to cover third parties, such as close relatives and spouses, which will be difficult to ensure. Patient and relative education is essential and possible in a well regulated system. Again there could be a problem with those close to a person receiving unrecognized xenotransplantation. **Another important provision is to make it compulsory for public health workers investigating an illness to ask whether the person had ever had a xenotransplant.** Finally, NHAs must have an effective event reporting system so that all the right links are made. That said, 70% of notifications to WHO are not reported by NHAs but by other agencies or the media. *It was agreed that in revising its guidance, WHO needed to ensure that the additional problems associated with xenotransplant surveillance are covered and that a proper link is made to the alert and response provisions.*

Session 6 – Conclusions and next steps

In concluding the work of the advisory consultation, the key information to be brought to the attention of NHAs included:

- a definition of xenotransplantation;
- the potential benefits for meeting the demand for transplants and recent progress in the field;
- limitations in current knowledge;
- potential infectious risks;
- the relative risks of unregulated transplantation versus regulated programmes; and
- a description of xenotransplant practices, initiatives, clinical trials, existing recognized clinical procedures and unproven commercial therapies.

NHAs should then be requested to:

- assess what is happening in their country;
- regulate any practices in proportion to the risks identified compared to the potential benefits, including the regulation of safety and efficacy, and ensuring quality standards in laboratories plus high standards of animal husbandry;
- ensure that there is good preclinical data to support any proposed trial;
- ensure that any proposed clinical trial is of a high standard and given proper oversight;
- provide education and information to the public; and
- state explicitly that unproven (commercial) xenotransplantation practices should not be performed.

Finally, the document should have a message to those performing xenotransplantation and include a link to the available documents.

The document developed for NHAs is appended (see Appendix 1). It was agreed that WHO should prepare a press release to accompany the document which, subject to normal clearance procedures, would be sent to all NHAs as soon as possible.

A report of the consultation would be prepared on the basis of which WHO would develop its action plan for the work identified by participants.

Dr Luc Noël then thanked all the participants for their hard work and contribution to the Consultation.

World Health Organization

Xenotransplantation: Hopes and Concerns

Transplantation is the treatment of choice for many serious diseases but is severely restricted by the shortage of available human organs, tissues and cells. Xenotransplantation offers a potential solution. It is defined as the transplantation, implantation, or infusion into a human recipient of living xenogeneic cells, tissues or organs, and human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with these living xenogeneic materials.

While animals are a potential source of high quality, readily available live organs, tissues or cells for transplantation, three problems need to be overcome, i.e. inadequate physiological function, rejection of the graft and the risk of transmitting a serious and/or novel infectious disease to the human recipient. Some very serious diseases such as AIDS and SARS have originated from animals and there has been transmission of viruses from xenotransplants using non-human primates. To date there is no evidence that xenotransplantation using other animals, such as the pig, has caused infections. However, xenotransplantation carries a potential risk of such diseases developing at some time. Such infectious disease may pose a major risk, not just to the recipient but also to the wider public because it may be transmitted, even across national boundaries.

Successful xenotransplantation of organs could benefit many people. Xenotransplantation of tissues and cells also offers a potential treatment of diseases such as diabetes and some degenerative disorders. There are some forms of xenotransplantation already in use, such as the treatment of severe burns with human skin cells cultured with mouse cells. Recent advances in the science of xenotransplantation, particularly using pigs, make it likely there will soon be more trials of new forms of xenotransplantation. Considerable effort has already gone into improving the effectiveness and to minimizing the risks. However, more pre-clinical studies are needed before xenotransplantation can be expected to deliver its many potential benefits.

On the other hand, there are xenotransplantation practices that are a matter of concern. Animal cells are being injected supposedly to achieve, for example 'rejuvenation' or as unproven 'treatments' for a variety of illnesses and complaints. In these unregulated practices, many types of animal cells have been used with little attention to quality, safety or effectiveness. These types of practices pose unacceptable infectious public health risks and should not be permitted.

Xenotransplantation poses potential public health risks to all Member States because of the freedom of people to travel. In May 2004, the World Health Assembly adopted Resolution WHA57.18, which urged Member States "to allow xenotransplantation only when effective national regulatory control and surveillance

mechanisms overseen by National Health Authorities (NHAs) are in place". It also requested the Director-General of WHO to support Member States in the development and regulation of xenotransplantation.

In order to implement the Resolution Member States are encouraged to:

- undertake an inventory of xenotransplantation practices in their country.

- only allow xenotransplantation if there is an effective regulatory system in place. Procedures should be regulated in proportion to the risks identified and with the aim of minimizing risks and improving safety and effectiveness.

- ensure that their regulatory authorities properly weigh the risks and potential benefits of any clinical trials or procedures before giving authorization; the likely benefits should be supported by evidence from appropriate pre-clinical studies;

- ensure there are regulatory standards relating to:
  - animal husbandry and the use of defined pathogen-free source animals from closed colonies;
  - authorization of procedures, ethical approval for clinical trials and consent procedures;
  - education of patients, intimate contacts and health care workers, including those in public health;
  - quality management of xenotransplantation procedures including laboratory testing; and
  - auditing of outcomes;

- ensure that there are effective surveillance systems in place which would identify and manage events which pose a potential danger to public health. WHO should be notified about major public health problems;

- ensure transparency about xenotransplantation activities; and

- promote public awareness.

Guidance on aspects of xenotransplantation and its effective regulation is already available from WHO at www.who.int/transplantation/xeno. There are links to other relevant websites and further detailed WHO guidance will be available shortly.

World Health Organization

Animal to human transplantation — future potential, present risk

Transplantation of animal organs, living cells and tissues into humans is termed xenotransplantation. Recent experiments have shown that the transplantation of organs from genetically modified pigs into baboons can yield moderate to good results and this raises hopes for the future of organ transplantation from pigs to humans.

However these, along with existing claims of treatments for diabetes or neurodegenerative disorders such as Parkinson's disease, are still at a very embryonic phase. Apart from a few simple, established procedures such as the treatment of severe burns with human skin cells cultured with mouse cells, xenotransplantation today is only acceptable in very tightly controlled human trials.

An advisory group of international experts has recently met at the World Health Organization (WHO) to discuss progress made in xenotransplantation. The main objective of the meeting was to propose ways in which the health agency can assist countries to implement stronger policies to control the practice and enforce quality and safety measures while still promoting further research into its potential uses.

The main risk in xenotransplantation is the transmission of diseases. Many serious infections in human history have originated in animals. Once a new pathogen is introduced in one individual, it may spread to the larger population.

To manage that risk, several countries have developed rigorous guidelines and oversight procedures for the performance of xenotransplantation. However, xenotransplantation is also carried out in countries that lack such oversight and where materials and procedures used have not undergone any quality and safety controls. This means there is no proof of the quality of source animals and no monitoring of the recipient, leaving no guarantee of the safety of the procedures for the patient. The problem is globalized when individuals travel to a country where xenotransplantation has no adequate oversight. The WHO advisory group notes that any xenotransplantation performed in countries without adequate oversight poses unacceptable infectious public health risks and should be stopped. International cooperation is clearly of paramount importance in the promotion of high standards for xenotransplantation across all regions. Without such oversight the efforts to minimize risks in some countries will be undermined due to increasing numbers of people travelling to countries with less stringent laws.

The potential for such risks led the Member States of WHO to adopt a resolution addressing xenotransplantation in 2004. The resolution urges member States "to allow xenotransplantation only when effective national regulatory control and surveillance mechanisms overseen by National Health Authorities are in place."

The WHO advisory group and WHO experts have concluded that stronger measures need to be put in place by countries to stop the illegal performance of xenotransplantation and to promote harmonized quality and safety controls. To harness the real potential of this promising field, while minimizing the risks of unproven or misused practices, they have revised an action plan to assist Member States to implement the WHO resolution by:

- updating a compendium of guidelines and recommendations for national health authorities and regulatory bodies to deal with xenotransplantation;
- improving methods for the collection and dissemination of information on xenotransplantation practices — successes and potential risks;
- raising greater awareness among national health authorities and promoting high ethical standards and well regulated practices.

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