Unclassified **DSTI/STP/BIO(2001)11/FINAL**

Organisation de Coopération et de Développement Economiques
Organisation for Economic Co-operation and Development **26-Oct-2001**

English - Or. English

DIRECTORATE FOR SCIENCE, TECHNOLOGY AND INDUSTRY
COMMITTEE FOR SCIENTIFIC AND TECHNOLOGICAL POLICY

DSTI/STP/BIO(2001)11/FINAL
Unclassified

Working Party on Biotechnology

OECD/WHO CONSULTATION ON XENOTRANSPLANTATION SURVEILLANCE: SUMMARY REPORT

This document is a joint OECD/WHO publication, which is also available under WHO code WHO/CDS/CSR/EPH/2001.1

JT00115450

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NOTE BY THE SECRETARIAT

This report summarises the topics, issues and considerations discussed at the OECD/WHO Consultation on Xenotransplantation Surveillance. The Consultation was held in Paris at OECD Headquarters on 4-6 October 2000 and was attended by over 60 participants from around the world, representing countries currently hosting xenotransplantation clinical trials; countries not actively engaged in xenotransplantation research but interested in its potential public health impact; and relevant international bodies such as the Council of Europe and the European Commission.

The report was prepared by Elettra Ronchi of the OECD Secretariat with the valuable contribution and input of Clara Witt, Temporary Technical Adviser to the World Health Organization (WHO), and the administrative and secretarial support of Alysia Ritter. The report is based on notes of the Consultation rapporteur, Louisa Chapman of the Centers for Disease Control and Prevention (CDC), Atlanta (Georgia, United States), whose expert assistance is gratefully acknowledged; and on transcripts of presentations, working group discussions and participants' comments.

The report was submitted to all participants for comments. Their support and advice is gratefully acknowledged.

The attached, revised version also includes changes submitted by the Working Group on Human Health-Related Biotechnologies and the Working Party on Biotechnology.

It was declassified by the Committee for Scientific and Technological Policy on 19 October 2001.

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EXECUTIVE SUMMARY

On 4-6 October 2000, the Organisation for Economic Co-operation and Development (OECD), the World Health Organization (WHO) and Health Canada jointly sponsored a Consultation on Xenotransplantation Surveillance. The Consultation was held in Paris at OECD headquarters and was attended by over 60 participants from around the world, representing countries currently hosting xenotransplantation clinical trials; countries not actively engaged in xenotransplantation research but interested in its potential public health impact; and relevant international bodies such as the Council of Europe and the European Commission. The purpose of the Consultation was to bring together epidemiologists, infectious disease specialists, clinicians, industry, government and international organisation representatives and others working in public health and xenotransplantation research to discuss and exchange ideas on the desirability of and possible approaches to xenotransplantation-associated infectious disease surveillance, both at country level and internationally.

In particular, the Consultation discussed the following questions:

- What is a xenogeneic infectious disease event, and what are some of the problems associated with the development of a standardised case definition?
- What can be learned about the characteristics of already existing and successful surveillance systems that might be applicable to the xenotransplantation setting?
- What are the particular characteristics associated with xenotransplantation that must be accommodated in any developed surveillance system for xenogeneic infectious disease events?
- What ethical considerations will need to be incorporated into xenogeneic infection/disease event surveillance systems?
- What might be a practical framework for international surveillance?

The format of the Consultation included formal presentations, round-table discussions, and a working group problem-solving session where participants were asked to discuss and generate recommendations on international xenogeneic infection/disease event surveillance.

Discussions at the Consultation indicated that significant scientific advances are rapidly paving the way to xenotransplantation. Current clinical trials include transplantation of foetal pig neural cells into human brains to replace cells lost to Parkinson’s disease or to stroke, and of pig pancreatic cells to treat insulin-dependent diabetes. Pig liver cells are also used to provide essential functions to patients waiting for human liver donations.

In light of the number of clinical trials and of the potential risk of xenogeneic pathogens, the overwhelming view of participants at the Consultation was that international surveillance for xenotransplantation-associated infectious disease is needed.

The main objectives of such an international xenotransplantation surveillance would be to:

- Rapidly detect and report xenotransplantation-derived infectious disease events particularly a rare event should it occur.
- Share information and co-operate.
- Facilitate xenogeneic disease event verification and response co-ordination.

Achievement of these objectives implies that countries willing to conduct trials for xenotransplantation agree to designate resources to establish a national xenotransplantation surveillance system as well as a national registry for xenotransplantation, and facilitate international exchange of information while protecting the confidentiality of individual patients and investigators. It also implies international consensus on the definition of xenotransplantation, on what constitutes a xenogeneic infectious disease event (including standards on laboratory results or diagnostic assays) and on norms for event reporting, including contingency plans. Common frameworks could promote international information sharing and co-operation and provide a mechanism to protect both public health and the need to respect human rights and dignity worldwide. International xenotransplantation surveillance would operate through an international framework linking designated national facilities. These would collect, analyse and report internationally relevant data. The *de novo* development of a totally autonomous international xenogeneic infectious disease surveillance system would offer little gain and preference should be given to the use of existing international surveillance systems, methodologies and tools. Synergy could be achieved by tapping into established resources. For example, the standardised vocabulary developed in MedDRA could be used as the language for detection and reporting, and the GPHIN system could be used for the rapid dissemination of information.

The WHO, in co-operation with the OECD and other relevant international bodies (*e.g.* the Council of Europe), was invited to take a leadership role in facilitating the development of internationally agreed norms for testing and reporting and the establishment of an effective xenogeneic infectious disease surveillance network. The network might be managed either by an organisation or by a consortium of network members with administrative functions under the supervision of a central secretariat. This secretariat could also act as an international safety monitoring board. Regardless of the format, it will be essential for the network to be owned by all its members, who would share its benefits as well as its costs and responsibilities.

KEY SUMMARY POINTS

The overwhelming view of participants was that international surveillance for xenotransplantation-associated infectious disease is needed. The main objectives of an international xenotransplantation surveillance would be to:

- Rapidly detect and report an infectious disease event, particularly a rare event, should it occur.
- Share information and co-operate.
- Facilitate xenogeneic disease event verification and response co-ordination.

In addition the Consultation concluded that:

- International consensus was needed on the definition of xenotransplantation, on what constitutes a xenogeneic infectious disease event (including quality assurance standards on laboratory results or diagnostic assays), and on event-reporting requirements and processes.
- The challenge faced in xenotransplantation will be to structure a case definition which encompasses known and identifiable signs and symptoms associated with xenogeneic infectious disease and recognises the potential for unusual, unexpected pathogens or for new expressions of infection or disease.
- Xenotransplantation surveillance might necessitate the development of a new paradigm for surveillance, *i.e.* not to expect known or anticipated clinical syndromes to drive surveillance but to actively search for unknown or unanticipated agents in the absence of recognisable clinical syndromes.
- Consideration should be given to selecting laboratory testing methods that feature the use of generic markers for categories of infectious agents, in addition to or in preference to laboratory methods based on detecting specific agents. The advantage of such generic assays is that they may detect variants for which standard assays may not be adequately sensitive, and can be used to look for agents not yet recognised. In many cases, however, these tests still require standardisation and validation, and may be costly because of the equipment, specialised reagents and skilled staff required. Thus, an effort towards sharing and co-operation on expertise and laboratory practices will need to be integrated in international xenotransplantation surveillance schemes. The possibility of designating – on a regional basis – accredited excellence centres to run such tests was considered.
- In general, the ICH guidelines may be applicable to xenotransplantation studies. However, a number of specific problems were indicated. Among these the most important are the attribution of causality of the event to xenotransplantation, evaluation of the public health implications, the timing of local contingency plan initiation, and determining when a local contingency becomes a national or international issue. It will be important to streamline reporting of SAE and to ensure – whenever possible – real-time review of safety data.
- For surveillance to be effective it must be acceptable, to the practitioners, the broader public, and governing bodies. Lack of acceptability results in delays in reporting and limited public dissemination of the information gained through surveillance due to political concerns.
- Maintaining surveillance successfully requires ongoing effort. Effectiveness requires regular feedback; adequate internal and external quality controls; continuous education and regular evaluation, both on how to report and on how to use feedback data in meaningful ways; and incentives and co-operation for reporting as well as guidance on the quality of reporting.
- Programmes to inform and educate the broader public are of critical importance and should be carefully planned together with those that will be primarily concerned with the implementation of surveillance schemes.

Countries are encouraged to:

- Establish national registries.
- Designate national xenotransplantation surveillance facilities.
- Enable linkage of national registries to corporate and international xenotransplantation registries.
- Adopt internationally agreed criteria for testing and reporting to ensure comparability of data.
- Facilitate free exchange of information among key stakeholders while protecting the confidentiality of individual patients and investigators.
- Provide the means by which non-confidential generic information for patient and public education could be easily derived and automatically updated.
- Develop programmes to inform and educate the broader public.

1. Introduction

On 4-6 October 2000, the OECD, the World Health Organization and Health Canada jointly sponsored a Consultation on Xenotransplantation Surveillance. The Consultation was held in Paris at OECD headquarters and was attended by over 60 participants from around the world, representing countries currently hosting xenotransplantation clinical trials; countries not actively engaged in xenotransplantation research but interested in its potential public health impact; and relevant international bodies such as the Council of Europe and the European Commission. The purpose of the Consultation was to bring together epidemiologists, infectious disease specialists, clinicians, industry, government and international organisation representatives and others working in public health and xenotransplantation research to discuss and exchange ideas on the desirability of and possible approaches to xenotransplantation-associated infectious disease surveillance, both at country level and internationally.

The Consultation was held as a result of recommendations made during a number of previous international meetings: a WHO Consultation on "Xenotransplantation: Infectious Diseases Prevention and Ethical Considerations"[1] held in 1997; the Canadian Forum on Xenotransplantation, also held in 1997; the OECD/New York Academy of Sciences Workshop on "International Issues in Transplantation Biotechnology, Including the Use of Non-Human Cells, Tissues and Organs" held in 1998;[2] and the United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) July 1999 workshop entitled "Infection Surveillance Post-xenotransplantation". The Consultation considered whether internationally co-ordinated xenogeneic infection/disease event surveillance was desirable, and discussed the following questions:

- *What is a xenogeneic infectious disease event, and what are some of the problems associated with the development of a standardised case definition?*
- *What can be learned about the characteristics of already existing and successful surveillance systems that might be applicable to the xenotransplantation setting?*
- *What are the particular characteristics associated with xenotransplantation that must be accommodated in any developed surveillance system for xenogeneic infectious disease events?*
- *What ethical considerations will need to be incorporated into such systems?*
- *What might be a practical framework for international surveillance?*

The format of the Consultation included formal presentations, round-table discussions, and a working group problem-solving session where participants were asked to discuss and generate recommendations on international xenogeneic infection/disease event surveillance.

The success of the Consultation was largely due to the active participation and willingness to exchange ideas and thoughts on the part of all those in attendance. The organisers of the Consultation are very appreciative of the work of the Co-Chairs, Mr. André La Prairie of Health Canada and Dr. Amorn Leelarasamee of Thailand, for their skilful leadership in keeping the Consultation on schedule while assuring that discussions were lively and pertinent. Thanks is especially owed to Dr. Louisa Chapman of the Centers for Disease Control and Prevention (CDC), Atlanta (Georgia,

1. For a copy of the Consultation report see www.who.int/emc-documents/zoonoses.

2. *Xenotransplantation, International Policy Issues* (OECD, 1999); also see the website http://www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm.

United States), for undertaking the demanding role of Consultation rapporteur. Without Dr. Chapman's willingness to assist the organisers, this report would not have been possible.

2. Surveillance Issues in Xenotransplantation

What is xenotransplantation?

Xenotransplantation is any procedure that involves the transplantation, implantation or infusion into a human recipient of live cells, tissues or organs from an animal source. Recently this definition has been extended in a number of countries to also include human body fluids, cells, tissues or organs that have had *ex vivo* contact with live animal cells, tissues or organs. The extended definition has, however, not been universally adopted.

Xenotransplantation has been proposed as an additional approach for alleviating the global shortage of human tissues and organs available for allotransplantation (the transplantation into humans of living cells, tissues or organs of human origin), or for providing treatment for diseases that do not respond to any other therapeutic intervention. Current clinical trials include transplantation of foetal pig neuronal cells into human brains to replace cells lost to Parkinson's disease or to stroke, and of foetal pig pancreatic cells to treat insulin-dependent diabetes. Pig liver cells are also used to provide essential functions to patients waiting for human liver donations.

2.1 Developing a case definition for a xenogeneic infection or disease event – do we need a new paradigm?

With xenotransplantation, there is a potential risk of transmitting known zoonotic infections as well as new or unknown infectious agents of animal origin into human recipients and into the wider human population. The latter is an unquantifiable hazard, although the probability of it occurring is potentially predictable, depending on the different applications of xenotransplantation. This raises a number of important issues to consider when developing a case definition. First, does the risk of transmitting infection from non-human species to the graft recipient and to the community in general outweigh the potential benefits of xenotransplantation? Is that concern realistic or a reflection of fears of the unknown degree of risk associated with this technology? Given that we have insufficient information about potential pathogens, is it possible to know when infection has occurred in the absence of specific tests? How do we monitor for infection?

The design of surveillance systems is traditionally based on the assumption that the infection or disease under surveillance can be defined. The challenge here is to accommodate the very real need to detect and discover both known and new or currently unknown infectious agents resulting from the practice of xenotransplantation.

There are still significant obstacles to xenotransplantation from an immunologic perspective. Hyperacute vascular and chronic rejection are still hurdles to be overcome. Because of these obstacles it is likely that xenotransplantation recipients will need significant degrees of exogenous immune suppression to maintain graft function in the human host. This means that many of the infectious complications of allotransplantation infection and malignancy could well occur in xenotransplantation. The unique feature of xenogeneic infections is that these may not be merely the typical opportunistic infections of allotransplantation, but rather could also include infections by potentially novel agents transferred from non-human species to humans.

In allotransplantation the risk for infection is seen as a simple equation which relates epidemiologic exposures to the net state of immunosuppression. The latter is a complex assessment of the individual patient's susceptibility to infection; it takes into consideration immunosuppressive therapy, the type of drugs and treatments administered, underlying immune defects, and other factors known to contribute to the risk of infection. Based on this experience, and on the fact that immunosuppressive regimens are fairly uniform in allotransplants, it is possible to predict what infections will occur and when following transplantation. Similar predictions cannot be made in the case of xenotransplantation, since the ability to predict and make a differential diagnosis depends on knowledge of the epidemiology of infection, on the standardisation of immunosuppressive regimens, and on appropriate assays for infectious agents - none of which is currently available.

It should be noted that even in allotransplantation many new pathogens have been discovered in the last three to five years. For many of these there is no effective therapy. It is likely that as immunosuppressive regimens change, and as donor species change, there will be additional new pathogens. Few data exist to guide decisions. *Thus, the greatest potential risk to the community would come from unknown highly pathogenic organisms, organisms transmitted without clinical symptomatology, or organisms associated with novel unrecorded syndromes.*

What tools are there to discover novel syndromes? Can the traditional paradigm of surveillance apply?

It undoubtedly will not be possible to rely solely on traditional monitoring tools for xenotransplantation, because serologic assays are generally of little help in the immunocompromised host. It will be necessary to use advanced molecular or antigen-based diagnostics. Moreover, the search for pathogens will need to be prospective as well as retrospective. Surveillance must actively search for the presence of both known and unknown or unanticipated agents in xenotransplantation product recipients, even in the absence of recognisable clinical disease syndromes. Thus, a new approach is necessary. Lessons learned with porcine viruses might be useful.

It follows that a new, broader case definition for xenosis or xenogeneic infection should be developed, one that recognises the potential for unusual, unexpected pathogens, or for new expressions of infection or disease. The definition, and the surveillance tools, should take into account such particular attributes as the level of immune suppression in a recipient and the length of xenotransplantation product exposure, and not be limited to a preconceived understanding of an infectious agent's behaviour in the xenotransplantation environment.

2.2 Surveillance from a virologist's perspective

One of the possible risks of xenotransplantation is the transmission of animal, particularly porcine, retroviruses to man.

In view of the possibility that co-expression of porcine and human retroviral sequences in the same cell might lead to retroviral recombination and the generation of viruses with new properties, the monitoring of patients undergoing clinical trials should be possibly not restricted to specific tests for PERV DNA and RNA. It should include procedures – such as amplification-based tests for particle-associated reverse

transcriptase (RT) – that can improve the detection of any viral or bacterial particles, as were used in early clinical xenotransplantation studies.[3]

In case tests with such non specific assays test positive, procedures developed for the identification of unknown retrovirus particles present at low concentrations could be employed. Thus, consideration should be given to selecting surveillance system laboratory testing methods that feature the use of generic markers for categories of infectious agents in addition to or in preference to laboratory methods based on detecting specific agents. The advantage of such assays is that they may detect variants for which standard assays are not adequately sensitive, and can be used to look for agents not yet recognised.

There are a number of specific *assays available to monitor for infections – over time the preferred monitoring method may and should evolve and vary. Flexibility should be an essential feature of any surveillance system, in terms of both approach and testing methods. As new pathogens are identified, they should become part of the standard repertoire for which surveillance is conducted. Thus, there is a need for both a traditional surveillance system and a proactive research programme aimed at addressing the same kind of issues. For example, identification of endogenous retroviruses would be greatly facilitated if the entire genome of the pig were defined. However, approaches for validating test methods as they develop and for assuring the quality of testing practices should be defined. International adoption and mutual recognition of such approaches should be encouraged.*

2.3 Existing surveillance systems as potential models for xenotransplantation

Regardless of its overall design, a surveillance system for xenotransplantation will need to possess many of the characteristics essential to any successful surveillance system.

Outlined below are a number of surveillance systems that could prove relevant for xenotransplantation, in that they could perhaps usefully integrate case reporting on xenosis or xenogeneic infection.

2.3.1 Pharmacosurveillance systems: the European Union Drug Regulatory Authorities Network

Although pharmaceutical products undergo extensive testing and review by means of controlled clinical trials prior to marketing, such trials have inherent shortcomings. They seldom involve more than 2 000 patients or last for more than three years; thus, uncommon side-effects or delayed effects of long-term administration may not be detected. In addition, most patients enrolled in clinical trials have relatively uncomplicated diseases and are drawn from restricted groups. Accordingly, premarketing data often do not apply to the elderly, pregnant women, children, or patients with more than one disease and who require treatment with multiple drugs. Such patients, however, are among those most likely to be exposed to a drug after marketing begins. Postmarketing surveillance is therefore crucial for providing additional safety information that cannot realistically be collected before approval of a drug[4].

The fundamental challenges of postmarketing surveillance, or pharmacovigilance, are risk detection, risk management decision-making, and risk communication and reassessment. A key component of pharmacovigilance is the reporting of adverse drug reactions (ADR). ADR reporting was conceived as a

3. Walid Heneine, Annika Tibell, William M. Switzer, Paul Sandstrom, Guillermo Vazquez Rosales, Aprille Mathews, Olle Korsgren, Louisa E. Chapman, Thomas M. Folks and Carl G. Groth (1998), "No Evidence of Infection with Porcine Endogenous Retrovirus in Recipients of Porcine Islet-cell Xenografts", *Lancet*, Volume 352, No. 9129, pp. 695-9.

4. McGettigan, P. and J. Feely (1995), *Pharmacoepidemiology and Drug Safety*, 4, pp. 355-358.

direct response to the failure to recognise thalidomide phocomelia until around 10 000 foetuses had been affected. A notification system could have recognised the association of a specific drug with a very rare disorder at least three orders of magnitude more effectively. Acknowledgement of the need for a global pharmacovigilance system and the public debate on the safety profiles of a number of drugs have resulted recently in an impetus for international co-operation.

Various steps have been taken towards international harmonisation of ADR reporting. For example, under the Council for International Organisation of Medical Sciences (CIOMS) and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (referenced as ICH), agreement has been reached with regard to specific terminology (*e.g.* definitions of "serious", "expected", and "listed"). There has also been harmonisation of data elements considered important in carrying out medical assessments of individual cases. The development of a Medical Dictionary for Drug Regulatory Activities (MedDRA)[5] and its translation into a number of languages are of vital importance. Pharmacovigilance guidelines and an infrastructure for reporting adverse events (AEs) involving pharmaceuticals now exist under the auspices of the ICH between Europe, the United States and Japan. Equally vital is the harmonisation of the international electronic exchange of individual case safety reports. Implementation of the specifications for that exchange, in line with the recommendations of the ICH, has produced a radical change in the way pharmacovigilance is conducted in the European Union.

The responsible agency in Europe[6] is the European Agency for the Evaluation of Medicinal Products (EMEA). The EMEA was created after the new regulation for approval of medicinal products in Europe became operational in 1995.

This regulation foresees two different procedures: a centralised procedure, which is run by the EMEA and is mandatory for biotechnology products; and a "mutual recognition" procedure applicable to the majority of conventional medicinal products and conditional on consultation between different member states in the Union (for more information see http://pharmacos.eudra.org). The EMEA is responsible for co-ordinating supervision of medicinal products that have been authorised within the European Community. Furthermore, the agency is responsible for providing advice on the measures necessary to ensure the safe and effective use of these products, in particular through evaluation and reporting of information on adverse reactions through a pharmacovigilance database. The number of adverse reaction reports related to nationally authorised medicinal products, including those authorised through the mutual recognition procedure, can exceed 100 000 reports per year (EMEA/PhVWP/2058/99FINAL).

To co-ordinate supervision of medicinal products between the central authority and the national authorities, the EMEA has set up in 1995 a data processing/communication network interlinking all competent EU authorities dealing with both human and veterinary products – Eudranet. The network has been fully operational in the European Community since 1998, and in the year 2000 it was extended to include Norway and Iceland. Eudranet provides a secure communication infrastructure or gateway, called Eudrasafe, to allow communication between national experts, industry, the central agency and national member states on all regulatory, scientific and pharmaceutical product information, relevant to pharmacovigilance.

Following the recommendation of the ICH to define standards and establish a common procedure for the exchange of adverse drug reactions, a first European pilot on pharmacovigilance was approved by the Committee for Propriety of Medicinal Products in 1999.

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5. MedDRA is designed for the classification, retrieval, presentation and communication of medical information throughout the medical product regulatory life cycle.

6 . Article 51(c) of Council Regulation (EEC) No. 2309/93 as amended.

The goals of this pilot were to improve data management on adverse drug reaction information, and to test key components of the European-wide electronic system for early warning via a www bridge, including the use of common terminology based on MedDRA. The electronic pharmacovigilance reporting system is expected to be fully operational by 1 January 2003.

The European Agency for the Evaluation of Medicinal Products, seven different member state regulatory authorities in Europe, and several pharmaceutical industries actively participated in the pilot.

The core requirements for the EU pharmacovigilance system have been defined as follows:

1. Establishment and maintenance of an operational database on adverse drug reactions.
2. Establishment and maintenance of an internationally agreed format for pharmacovigilance data.
3. Recording and archiving of data exchanges to allow traceability.
4. Remote access of the system via web technology.
5. Secured message exchange with authentication, non-repudiation and encryption.
6. Integration of different medicinal product and medical dictionaries.
7. Tools for expedited or periodic reporting.
8. Flexible infrastructure to take account of further improvements or adjustment.

The pilot tested a number of these key elements – in particular points 1, 5, and 6 – deemed necessary for successful pharmacovigilance.

From the very start of the pilot, however, it became apparent that conversion of a paper-based reporting system of ADR data to electronic transmission and traceability were particularly complex issues. To enable this transition, a combined system was developed to allow both types of communication.

The pilot will soon be extended to include the United States Food and Drug Administration (FDA) pharmacovigilance network, *i.e.* the MedWatch network and database.

The FDA's MedWatch programme is designed for the targeted reporting of serious adverse events and problems with medical products, so that these can be monitored. In addition MedWatch works to ensure that new safety information is quickly communicated to the health professional community and to consumers. The programme aims to enhance post-marketing surveillance of medical products as they are used in clinical practice, so that the FDA can, as rapidly as possible, identify serious reactions and hazards associated with these products. Although it is mandatory to report to the FDA serious adverse events[7] (SAEs) involving drugs investigated in clinical trials, SAE reporting to MedWatch during the

7. According to CPMP/ICH/377/95, "Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting":

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product ***and which*** *does not necessarily have to have a causal relationship with this treatment.*

A serious adverse event or reaction is ***any untoward medical occurrence*** *that at any dose:*
- Results in death
- Is life threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

premarketing phase is *entirely optional*. This is not the case for the European network system, Eudranet which, according to the common position stated in the European Parliament Session Document C5-0424/2000[8], has been conceived for the regulatory transfer of information between any company and any authority in Europe during *the whole life cycle* of a medicinal product.

In light of Commission Communication 98/C 229/3, a xenogeneic cell therapy product can be classified in Europe as a medicinal product.[9] In addition, a draft European Directive on good clinical practice calls in its current version for a centralised clinical trial approval procedure of xenotransplants, gene therapy stem cell products. Thus, Eudranet could potentially be used for the surveillance of xenotransplantation, particularly xenogeneic cell therapy products in Europe.

In the United States, on the other hand, FDA has not deemed MedWatch adequate for xenotransplantation surveillance, and has developed and is testing a database and reporting system specifically for all xenotransplantation products and procedures.

2.3.2 Clinical trial surveillance systems: expedited reporting

As mentioned above, pharmacovigilance guidelines and an infrastructure for reporting AEs for pharmaceuticals exist under the auspices of the ICH between Europe, the United States and Japan. The ICH guidance expanded the pre-existing national systems to include both investigational and marketed drugs, and included standard definitions and terminology for clinical safety reporting.

Within this guidance, there is a requirement for expedited reporting of SAEs that are both unexpected and possibly related to the study drug. This applies to both spontaneous postmarketing reports of ADRs and reports from any type of clinical or epidemiological investigation independent of design or purpose. Expedited reporting requires that the regulatory authorities be informed of fatal or life-threatening unexpected SAEs within 7 days, and other serious and unexpected adverse events within 15 days. Follow-up information must be provided as soon as it becomes available. The purpose of expedited reporting is to make regulators, investigators and other appropriate parties aware of new, important information on serious events. Investigators are required to report any SAE immediately to the sponsor of the trial, who then informs all other investigators involved in the trial, the relevant regulatory authorities and ethics committees/investigational review boards (IRBs). There are standard formats for reporting such as those set by MedWatch in the United States and CIOMS in Europe. The timeline for reporting of AEs should be agreed upon with the sponsor and specified in the protocol. The sponsor is, in general, also required to report all SAEs to the national regulatory authority and to other investigators in the trial. In the United States the principal investigator is responsible for notification.

In general, the ICH guidelines should be applicable to xenotransplantation studies. Indeed, surveillance activities according to ICH guidelines have been incorporated into a number of the xenotransplantation clinical trials currently under way. For example, Novartis has Standard Operating Procedures (SOPs) for clinical trials that could also be applied to xenotransplantation trials. These SOPs include strict timelines

8. As stated in the Directive of the European Parliament and of the Council on the "Approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use". Article 14 stipulates that it is also necessary to make provision for the monitoring of adverse reactions occurring in clinical trials using Community surveillance (pharmacovigilance) procedures in order to ensure the immediate cessation of any clinical trial in which there is an unacceptable level of risk.

9. Concept Paper on the development of a Committee for Proprietary Medicinal Products (CPMP): Points to Consider on Xenogeneic Cell Therapy, 16 November 2000, CPMP/BWP/3326/99.

for the reporting of SAEs by the investigators to their IRBs and to the sponsor, and for the processing and review of the reports by the company's Clinical Safety Department, prior to submitting the reports to the regulatory authorities, other investigators in the study and the ethics committees. More specifically, if an SAE occurs, the company needs to be notified within 24 hours; notification could be as simple as a telephone call or fax. As soon as the company is notified, the information is sent to the Central Safety Department at the company's headquarters for review – within 48 hours for life-threatening events and five days for other SAEs. The company is responsible for informing the appropriate national authorities within the defined ICH timeframes (*i.e.* seven or 15 days). These procedures, however, are not standard requirements and may vary from company to company. Follow-up reports for SAEs have to be submitted when a final diagnosis is not known at the time of the initial report or if there has been a change in the diagnosis or causality assessment. Non-reportable SAEs have to be processed by the company within 20 days. It should be noted that reporting of SAEs is in general currently confidential and not placed in the public domain.[10]

For transplant studies the average incidence of events is relatively high compared to other clinical trials: approximately 15-20 AEs per patient per year, of which 4-8 are in general SAEs. This is because clinical studies in transplantation are complex, and factors such as the surgical procedure and immunosuppressive regimens contribute to the adverse event profile. For xenotransplantation, due to the more complex immunosuppression and the combinations of immunosuppressants not normally used in clinical practice, it may be anticipated that the total number of SAEs will increase. Moreover, some of the immunosuppressive drugs may be experimental themselves. There may also be unknown effects of porcine microbiological agents. Attribution of causality and specificity to the xenotransplantation procedure will therefore be difficult to determine.

It is important that clinical trials are overseen by, *e.g.* an independent multidisciplinary safety monitoring board that would review all safety information across all studies. This could be performed via periodic updates, although the board could be notified on a *real-time basis* for potentially important xenogeneic events.

In addition, the system of adverse event reporting would need to be streamlined for both AEs and SAEs certainly for the initial trials, for example with simultaneous transmission of reports to the local company and the central safety department for verification and with rapid turnaround. Submission to the appropriate local regulatory authorities might need to proceed within a reduced time frame compared to the one envisaged by ICH, as SAEs may need to *be communicated in real-time.*

The cascade of safety information to other regulatory authorities and supranational bodies should be the responsibility of the local regulatory authority. In countries where the required infrastructures do not already exist, it may be desirable to develop links with extra-national or international bodies that can assist in performing the needed tasks.

10. A recent US FDA rule was proposed on 18 January 2001 that would require sponsors of gene therapy and xenotransplantation INDs to submit redacted versions of their files that would then become publicly available. If the rule is approved it is conceivable that SAE notifications could be placed in the public domain.

Other specific problems with assessing AEs may be anticipated. Among these the most important are the attribution of causality of the event to xenotransplantation, evaluation of the public health implications, the timing of local contingency plan initiation, and determination of when a local contingency becomes a national or international issue.

2.3.3 Examples of current surveillance strategies in industry-sponsored xenotransplantation clinical trials

In order to eliminate or reduce the risk of infection or disease resulting from the xenotransplantation procedure, surveillance activities of the following three populations have been (and might need to be) included in trial proposals:

1. Recipients of xenotransplantation products.
2. Sexual or close contacts.
3. Donor animals, traceable from recipient to source animal.

The majority of the surveillance activities currently proposed for clinical trials are laboratory-based. Laboratory surveillance has in general been structured around frequent testing for evidence of infection with specific agents (most notably porcine endogenous retrovirus, or PERV) for five years following the transplant, then at appropriate intervals for the life of the xenotransplantation product recipient. Laboratory testing employs a variety of virus-specific assays, which should be validated where possible.

Apart from the possibility of PERV infection, contingency plans have been considered and need to be in place in the event that a patient presents with an unexplained prolonged (over one week) fever of unknown origin (FUO) or an unexplained syndrome suggestive of infection. In such an event, a number of steps would be undertaken:

1. Exclude symptoms that might normally be associated with allotransplantation, or with side-effects of immunosuppressive drugs.
2. Exclude PERV infection by PCR/RT-PCR testing.
3. Review other recipients of cells, tissues or organs derived from the same cohorts of pigs.
4. Review close contacts for similar signs or symptoms.[11]

If results indicate that the prolonged FUO or unexplained syndrome is probably linked to the xenotransplantation procedure, relevant trials would be stopped while the case is further examined. To check for the transmission of both known and unknown pathogenic agents, testing might include PCR tests

11. Although the definition may vary from country to country, the term "close contact", in this setting, is usually interpreted as being a person who lives in the same household or has intimate contacts with the recipient of a xenotransplant. It should be noted that there is no universal agreement on the need to survey or monitor sexual or close contacts. Many feel it is appropriate to monitor contacts only if infection has been established in recipients.

with degenerate primers[12] and co-cultures. Archived pig samples would also be tested. Isolation of the patient could become necessary. A number of OECD countries have quarantine laws that allow detention and isolation (for limited and defined periods of time) of patients who represent an acute, short-term, certain and casual threat to other individuals and therefore to public health. *However, even when voluntary compliance has failed, isolation of patients, especially long-term isolation, which may be contemplated in case of a serious threat to public health, is particularly difficult to enforce. Prospective isolation without proof of both infection and potential for casual transmission might not only be difficult but impossible, and is of questionable efficacy.*

If the causal agent is identified the clinical trial might resume, provided that the patient's illness resolves and that there is no evidence of transmission of an untreatable syndrome or infection. In addition, the relevant herd of source animals would have to be shown free of the agent. Appropriate approval from the public health authorities for resumption of the trial would be necessary. If the aetiology of the syndrome is not identified, continued review of the patient and data would need to be performed by the appropriate experts.

To date, informed consent documents provide for either mandatory or recommended long-term follow-up, condom use, notification of close and sexual contacts, and archiving tissue and blood samples, as well as reporting of information to a national database. Recipients are asked to consent to lifelong monitoring. Consent for autopsy or specific tissue biopsy and subsequent archiving is also sought. Prior consent for autopsy is, however, not universally enforceable over the wishes of surviving family members, and compliance cannot be guaranteed. In general, informed consent documents are seen as a way not only to inform but also to educate a prospective xenotransplant recipient and close contacts.

A significant problem identified with xenotransplantation surveillance activities during clinical trials has been their high cost. In general, the cost of clinical xenotransplantation trials is expected to be significantly greater than those of most other types of clinical trials, including those for gene therapy. Nevertheless, the expressed intent of the industry sponsors is to continue to monitor through the postmarketing phase – although in time, depending on outcomes and advances in knowledge, the frequency and duration of testing might be shortened. However, current surveillance systems of clinical trials have been designed with the belief they are sustainable, and with the intent of sustaining them.

2.3.4 Infectious disease surveillance systems

Network for the epidemiological surveillance and control of communicable diseases in the European Community

In 1998 a decision was made by the European Parliament (Decision No. 2119/98/EC of 24 September 1998) to set up a legal framework for epidemiological surveillance and control of communicable diseases in the European Community. The Decision confers on the Commission the

12. As mentioned in a previous section, amplification-based tests for particle-associated reverse transcriptase (RT) whose sensitivity is comparable to that of PCR for viral RNA, might improve detection of viral or bacterial particles that are causing the syndrome and are capable of reverse transcription. For example, a presence of only fragments of PERV RNA in recombinant particles might be missed by PERV-specific PCR, which assesses only a small genome fragment, while it would be detected by degenerate primers. In case of positive results with such assays, procedures developed for the identification of unknown particles present in low concentrations could be used to determine their identity and composition. This approach might also signal transmission of other, hitherto unidentified retroviruses.

responsibility for developing this network and facilitating and co-ordinating its various activities. The objectives of the system are to establish:

1. An early warning and response system.
2. Epidemiological surveillance.

In addition, the network provides a framework for a spectrum of other activities that contribute to the timely exchange of information and response for health protection (see Progress Report on the Network for the Epidemiological Surveillance and Control of Communicable Diseases in the Community – Brussels, 07.09.2000.COM-2000-471). The two objectives are closely interlinked although they are delivered through a separate mechanism. The Early Warning and Response System is based on a permanent telematic link. This system provides the competent public health authorities of the member states and the Commission with an efficient and rapid exchange of information on outbreaks or potential outbreaks of communicable diseases (the defining criteria are set down in Decision 2000/57/EC). This system is not intended to, nor does it, react to isolated incidents that do not have wider implications in member states.

Between July 1999 and May 2000, 13 disease events acquired within the Community and a similar number acquired outside the Community were reported through the Early Warning and Response System.

The system provides the information essential to take preventive action and, through investigation of the reported human cases, enables identification of control measures.

One of the main problems with the system is determining at which point notification of the potential outbreak should be made. When does speculation become a likely risk that should be communicated to the Community network? The responsible local authorities may not have immediately at hand all the information required to make an informed report, and premature declaration could trigger unnecessary alarm in other member states.

Routine exchange of information on outbreaks can occur through a variety of communication tools. However, the majority of information exchange within the network takes place via the Internet. The telematic link used for communicating is the "Health Surveillance System for Communicable Diseases" (HSSCD) within the European Public Health Information Network (EUPHIN) (similar to the Eudranet model).

All member states have requirements on transmitting information to the Commission on resurgence of all cases of communicable disease and on any control measure required, progression of epidemics, unusual epidemic phenomena or communicable disease of new or unknown origin. The latter requirement might also serve the purpose of xenotransplantation surveillance.

As mentioned previously, the second objective of the system is epidemiological surveillance. Epidemiological surveillance is being developed in the form of networks for 41 specific diseases or special health areas identified as priorities in Decision 2000/96/EC.

Reporting in the networks is principally based on links across existing surveillance institutes and structures in member states. The model for each of the existing disease-specific networks is one co-ordinating institute supported by the national institutes in other member states. It is envisaged that co-ordinating centres or hubs for each disease network will be responsible for the ongoing systematic collection, interpretation, analysis and dissemination of data and information.

The core components of Epidemiological Surveillance Activity are the following:

1. Disease-specific networks – dedicated to one or several diseases or special health issues of importance to the Community.
2. A routine surveillance network – collating routinely collected and available communicable disease surveillance data from member states.
3. Inventories – describing current systems of surveillance, prevention and control.
4. Zoonoses – reporting information or data on human zoonoses.
5. Information-sharing – an exchange area via Internet where relevant information can be shared between national authorities.

The Commission determines, with the assistance of member state representatives, the following:

- Case definitions.
- The type of data to be transmitted.
- Methodologies for epidemiological surveillance and laboratory tests.

The Legionella network (mainly for surveillance of travel-associated infections) is a useful case to review. It highlights the added value of supranational surveillance, since the country where the case is reported most often is not the country where the individual has acquired the disease, and cross-country communication becomes essential. In addition, Legionellosis is not a common disease, and the collation of information by the network helps detect clusters of sporadic cases and risks, perhaps providing a model for xenogeneic infection surveillance. The rapid sharing of information is essential for control and prevention of disease spread. Funded initially by the WHO and now by the European Commission, the Legionella network has been co-ordinated by the UK Communicable Disease Surveillance Centre (London) since 1993. Collaborators are nominated and approved by member states. The strengths of the network are:

- The already established link between the surveillance experts and the competent authorities.
- The internationally established and recognised external quality assurance scheme.
- Real-time telematic exchange of data.

In conclusion, lessons learned from supranational surveillance systems highlight that such systems are ultimately sustainable only if the information which is monitored provides clear added value to the global community.

In addition, supranational surveillance depends critically on:

- Dedicated resources for the network activities.
- Agreed methodology, clear objectives, agreed methods of reporting and disseminating information.
- Co-operation with other surveillance organisations to avoid duplication of efforts.
- Annual re-evaluation of case definitions as diagnostic methods progress and knowledge advances.

Finally, sharing and co-operation are key to the effectiveness of any surveillance at the international level. It is therefore very important to develop a methodology to protect security and confidentiality of data. It is critical to have secure exchange of information in order to protect confidentiality and retain trust and co-operation between all stakeholders.

3. Ethical considerations in xenotransplantation surveillance

Recent public reaction to a number of applications of biotechnology, particularly in the agro-food sector, have shown that discussion with the public on social and ethical issues is a key element in the process of adopting any new technology.

This is particularly true for xenotransplantation. It has become clear that a broad range of ethical implications, including the feasibility of xenotransplantation and of the surveillance schemes, will have to be addressed.

Faced with uncertainty, it is difficult for the general public to evaluate the tradeoffs necessary in xenotransplantation, *i.e.* to judge what balance is acceptable between expected risks and benefits. In addition, there are other unresolved questions:

1. Protection of patients' privacy and confidentiality.
2. Conflicts between private vs. public interests.
3. The potential for infringement of the human rights of first recipients.
4. Intersection between domestic and international law.
5. Appropriate action in the case of xenogeneic infection.

In considering the above, three questions seem particularly relevant to advance the debate on ethical issues:

1. How can the public be engaged in a meaningful way?
2. What kind of consent process is appropriate for potential xenotransplantation recipients, particularly those included in the early trials?
3. Are there any types of limited clinical studies that can answer important scientific questions while substantially minimising the risk to the public (*i.e.* can we reduce the harm-benefit threshold)?

It appears that xenotransplantation raises issues that are not adequately covered by current international guidelines, including those of the Council for International Organization of Medical Sciences on Biomedical Research Involving Human Subjects or on the Ethical Review of Epidemiological Studies.[13]

To date, most ethical debates have primarily focused on scientific ethical issues pertaining to the first required level of ethical analysis of clinical research, usually discussed under the rubric of "beneficence" in the 1979 "Belmont Report" of the US National Commission [14] on the "Protection of Human Subjects of Biomedical and Behavioral Research" and in the regulations of respective nations and in official reports on the ethics of xenotransplantation from the United States and the United Kingdom.[15] Even in such cases the interconnections between clinical trials involving xenotransplantation and the ethical principles and applications of the principles in the Belmont Report are far from obvious.

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13. International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva, CIOMS 1993. International Guidelines for Ethical Review of Epidemiological Studies, Geneva, CIOMS, 1991.

14. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (1979), "The Belmont Report", *Federal Register*, Vol. 44, pp. 23192-23197.

15. Institute of Medicine (1996), "Xenotransplantation: Science, Ethics, and Public Policy". Washington, DC: National Academy Press, pp. 10-11. Advisory Group on the Ethics of Xenotransplantation (UK), (1997), Animal Tissue into Humans. (Kennedy Report), London: Stationery Office.

A main issue is how to assess the public implications of an event for which the risks are relatively unknown but the consequences are potentially disastrous, a predicament often referred to as the "China Syndrome".

Currently the informed consent requirements for patients who might receive the first xenotransplants exceed those in any known research setting. In some guidelines they entail commitment on a number of issues that may most likely affect the patients' overall integrity as individuals. In addition, the prospective participant in a xenotransplantation trial is likely to be very ill. Yet, if their autonomy is to be respected, they will need to understand and weigh tradeoffs and make decisions.

An important component of consent is complete and honest disclosure of information, which must be provided in such a way that the patient can be educated and understand the risks and benefits of the procedure. In the case of xenotransplantation procedures, however, information about the possible outcomes may be incomplete or altogether unavailable. In addition, a terminally ill patient's ability to make a free choice may be severely impaired.

There are other difficult questions for which there are as yet no satisfactory answers.

A major one is what to do if a patient changes his/her mind about invasive monitoring to which he/she agreed as part of informed consent, since informed consent is not binding and a patient has a right to change his/her mind prior to the procedure. Historic precedents of situations of this sort are uncommon. One potentially applicable approach is referred to as "The Ulysses Contract". In this situation, a person binds him-/herself in advance to a future therapeutic course of action. Such contracts have been advocated, for example, for patients with severe bipolar disease who fluctuate between ability and inability to consent, to allow treatment against their will when the need arises at a later time when they are not competent to consent.

However, in the case of xenotransplantation, such binding consent would be enforced also to protect others, not only the actual contractors.

A number of additional questions laden with ethical challenges are the following:

1. Who will trigger and enforce action in response to surveillance?
2. How will (or simply, *Will*) compliance with surveillance be ensured?
3. What standards are appropriate to declare an individual incompetent either to originally give consent, or to co-operate in the long term?
4. What if the recipient or the intimate contact refuses to co-operate?
5. To what extent is the consent legally enforceable?
6. Will laws be enacted in advance of clinical trials?
7. What would constitute compelling evidence of a public health threat if experts disagree, *i.e.* burden of proof?

Finally, there are several areas where conflicts of interest may arise. The Declaration of Geneva of the World Medical Association binds the physician with the words *"the health of my patient will be my first consideration"*, and the International Code of Medical Ethics declares that *"a physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient"*.

This may place physician and public health authorities in conflict if an infection is identified in an individual recipient. In addition, the Helsinki Declaration on Ethical Principles for Medical Research Involving Human Subjects states that in medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

Xenotransplantation clinical trials present situations that may place the interests of recipients and the greater good of society at odds. These situations need to be thoroughly explored and publicly debated.

4. Tools and characteristics desirable for xenotransplantation surveillance

4.1 The specialised issues of early detection and response

Early detection and reporting capability should be essential features of any surveillance system developed for xenotransplantation. The system should provide rapid access to information about xenogeneic infection and disease events or threats, so that public health action can be initiated in a timely and effective manner.

There is, however, an unavoidable trade-off between the need for immediacy in detection and reporting, and the need for certainty about the information being reported. The information gained and reported early from a surveillance system may not be sufficiently validated because of the time required for any confirmation through investigation. Also, for the sake of timeliness, early information may not be sufficiently complete to accurately describe an event. The surveillance information produced may not even be that which is really wanted or ultimately necessary for good decision making. (This results from the constraints inherent in traditional surveillance systems and retrospective analysis.) On the other hand, speed in detection and reporting will be essential when conducting surveillance for a highly pathogenic and transmissible infection or disease. It may be extremely inappropriate to wait for time-consuming validation and confirmation of a detected event before making public health decisions.

For xenotransplantation, striking the right balance between speed in reporting and validation of the information is made even more difficult because much is still unknown about potential xenogeneic infections and diseases. Knowledge of the infectious potential of an unexplained syndrome or infection (for example, whether it will inevitably be fatal, or have transmission potential) and the likelihood of its occurrence is important. These factors will also have an impact on the acceptability of a rapidly detected and reported but false-positive event – and on the acceptability of the inverse, a late detection and report of a truly occurring public health hazard.

The speed with which an event is reported will inevitably be influenced by the "detectability" of an infectious agent or disease, and by how much emphasis is placed on the validation processes. Yet, "detectability" may not be a good predictor of public health impact. This problem can be obviated to some extent by the use of modern diagnostic and communication technologies that enable and could facilitate rapid detection, verification and reporting. It will be important, however, that these new technologies are not overwhelmed by inappropriate use or irrelevant tasks. Their use must remain focused and the surveillance system must remain efficient and credible.

Two surveillance tools, the Canadian Global Public Health Intelligence Network system and the US Public Health Service's pilot National Xenotransplantation Database (US PHS NXD), have been developed to address the need for both rapid communication and traceability of infectious events. They are reviewed below.

4.2 Rapid communication: the Canadian GPHIN

An example of a rapid communication tool useful to public health surveillance is the Global Public Health Intelligence Network (GPHIN), developed by Health Canada's Laboratory Centre for Disease Control (LCDC) with assistance from the World Health Organization. GPHIN is an early warning, real-time, Internet-based system, which continuously scans electronic sources of information on global public health events. The network is part of a larger Health Canada project – the National Health Surveillance Infrastructure, or NHSI. The programme is made up of seven pilot projects designed to demonstrate the use of technology in healthcare information systems.

GPHIN collects information from about 600 (mostly Internet-based) information sources, including list servers, bulletin boards, news services and international and non-governmental organisations.

It is essentially an Internet browser. It identifies and extracts outbreak reports from the electronic media using keywords assigned by the LCDC. The system continually scans for news of any outbreaks of 31 communicable diseases, as well as for articles about natural disasters and drug-resistant pathogens. Thus, GPHIN also covers non-communicable diseases, food and water safety, environmental health risks, and the health impact of natural disasters.

As soon as an outbreak is identified, the information is used by international public health officials at the World Health Organisation, who are responsible for verifying the problem and for the public health response (see below). The general public does not have access to the information.

The system identifies, on average, five new outbreaks every day.

Information can be queried by time or by classification of disease. Stored information can be searched by topic, and an abstract and score on the accuracy of the information is also provided.

Early warning of significant public health events comes most frequently from non-WHO sources (75%). Between November 1999 and October 2000, 228 outbreaks or public health events were detected by GPHIN. Of these, 74.1% of the reports were verified and about 26% were unverifiable. Failure of verification may be due to inaccurate information or to lack of access to information. Information is disseminated to relevant public health agencies and to key international public health professionals. GPHIN appears to be particularly useful in detecting unusual events, *e.g.* anthrax.

The quality of reports retrieved by GPHIN, however, can vary considerably. For example, as a non-evaluative tool, GPHIN may present reports out of context. Also, reports may be subject to information bias because of the uneven diffusion and use of modern information technology throughout the world, and because not all languages are equally represented in the news media or addressed by electronic search engines. Currently the system is bilingual, searching the Internet for sources in English and French. While these shortcomings are partly offset by the information received directly from the WHO network, as will be further discussed below, a more active dialogue with the field will lead to earlier detection of important events and events that escape identification.

4.2.1 The WHO outbreak verification process

To investigate and follow up outbreak reports from GPHIN and other sources, in 1997 WHO established an outbreak verification team that includes disease-specific experts who meet daily to review and discuss outbreak reports.

When the team receives an unconfirmed outbreak report, relevance to international public health is assessed and, if appropriate, further information is sought.

The verification team first determines if an event is of potential international public health importance on the basis of available background information, endemic levels, and details of previous outbreaks. *International public health importance has been defined as serious health impacts or unexpectedly high rates of illness and death; potential for spread beyond national borders; interference with international travel or trade; or the likely need for international assistance in disease control.*

Each event requires an individual assessment on the basis of these criteria, in particular when available information is insufficient to determine if an event should be classified as an outbreak (number of cases in excess of expected numbers). While some diseases will almost always be regarded as important in terms of international public health, *e.g.* Ebola hemorrhagic fever and cholera, others may not, depending on the circumstances.

Once an event has been deemed of potential international importance, the process of verification is initiated. This information is then shared via e-mail with designated contacts in WHO regional offices, who seek confirmation of details from health authorities in the countries concerned – usually through the WHO representative. The team may seek additional information from other organisations in the field, such as the International Red Cross, *Médecins sans Frontières*, and Medical Emergency Relief International.

Upon receipt of feedback, the team determines if the event meets the definition of an outbreak (*i.e.* the number of cases observed exceeds the expected number of cases in a given population for a given period). Reaching a final decision may require further consultation with the WHO regional office, the country representative, or health authorities in the country in question.

Timely dissemination of outbreak information to those who need to know is a key aspect of the response to the verification process, and details of outbreaks with potential for international public health importance are disseminated through various channels. Information is shared directly with partners for immediate action (epidemic response), but also routinely with a wider audience through the Outbreak Verification List, the WHO Disease Outbreak News on the World Wide Web, and the Weekly Epidemiological Record (WER).

The Outbreak Verification List is distributed weekly by e-mail to approximately 800 subscribers. The distribution list includes WHO staff worldwide, other UN agencies, national health authorities, field epidemiology training programmes, and non-governmental organisations.

The WHO Disease Outbreak News at http://www.who.int/emc/outbreak_news/index.html provides the public with information of international importance. Because Outbreak News is in the public domain, only information about officially confirmed outbreaks is disseminated.

The third mechanism for communicating this information is the WER. The report is published in French and English and issued in print and electronically (http://www.who.int/wer/index.html). It covers epidemiologic information on cases and outbreaks of diseases listed under the International Health Regulations (yellow fever, plague, cholera) and also on other communicable diseases of public health importance.

Finally, co-ordination of timely and effective epidemic response is intrinsically linked to dissemination of information about important disease outbreaks. During the verification process, WHO routinely offers technical assistance for the investigation and control of the event. Such assistance may range from advice (*e.g.* identifying appropriate laboratory facilities) to the deployment of field teams.

The median time between the reported onset of an outbreak and the team's receipt of the first report is about 18 days (from 1 to 215 days). This interval is similar for official and unofficial sources but may vary considerably for different diseases,[16] particularly for endemic diseases in the absence of established epidemic thresholds.

4.3 Databases and registries: the US National Xenotransplantation Database

The value of a xenotransplantation database lies in the possibility of surveying populations of recipients, identifying common outcomes and examining whether those outcomes have a common causal link. Such information could also provide the means for rapid recognition, accurate assessment and appropriate response to infections of recipients or other adverse events that may have public health consequences. The goals of such a database would also be to assist in identifying significant common epidemiological features among xenotransplantation product recipients; to enable the identification of the incidence and clustering of adverse health events; and to provide a framework for safety assessment of patient outcomes.

An international electronic database of recipient information would be an even more powerful public health surveillance tool. With larger populations surveyed, there is a greater probability of recognising rare or uncommon associated health events.

Electronic repositories may come in different formats: text files, spread sheets, images or databases.

Electronic databases, with the current state of technology, are perhaps the best type of repositories for surveillance because they can enable analysis across fields and subject areas. They also facilitate indexing of raw or verbatim text against chosen vocabularies and can facilitate storage and retrieval of raw data as well as its indexing. In addition, electronic databases support data mining and analysis.

Since 1997, the United States has been developing a dedicated National Xenotransplantation Database (NXD). This database is a model for a national data collection system or network for detection, identification, monitoring and evaluation of xenozoonotic risk. The main functions of the database are to:

1. Provide assessment of long-term safety.
2. Identify epidemiological significant common features among xenotransplantation product recipients.
3. Recognise rates of occurrence and clustering of health events on a national level.
4. Provide a framework for assessment of patient outcomes.

A key aspect of the database is its software components. These are based on Oracle tools and include specifically designed data entry modules, computer-assisted coding, a browser for scanning information, *ad hoc* queries of commercial products and preformatted reporting modules.

Short-term surveillance is carried out through on-line record analysis. By using *ad hoc* or off-the-shelf query and statistics tools such analysis can be extended to include long-term determination of trends.

The system is now in a pilot form. The pilot study's key goal is to define the information needed for surveillance and particularly the data required from sponsors of clinical trials. After further development and enhancements, it is intended that the NXD will compile data from all sponsors conducting trials in

16. Thirteen to 15 days (median) for acute hemorrhagic fevers, anthrax, and cholera; 20 to 35 days (median) for yellow fever and plague; and >50 days (median) for acute respiratory syndrome and meningococcal disease (*http://www.cdc.gov/ncidod/eid/vol6no2/grein.htm).*

xenotransplantation. Sponsors will submit information from clinical centres conducting the trials and from facilities supplying xenotransplantation products for clinical use. It is planned that the database will function as an information repository, as a means of reviewing information, conducting short-term analyses, and supporting longer-term statistical analyses. The database is configured for future integration with other relevant FDA/CBER databases.

Data-sharing and standardisation are required for the successful implementation of the database. The FDA is therefore developing a standard data model and a dictionary. Adverse event data will be collected in a manner consistent with the ICH-developed E2B standard for safety information. The choice of terminology to integrate in the database suggests a need for a dynamic and flexible vocabulary that can evolve as knowledge on xenotransplantation potential outcomes and risks progresses. To that end, indexing of information and terminology is based on the Medical Dictionary for Regulatory Affairs (MedDRA).

In developing the system, two key features of the database were identified: it would need to effectively recognise health risks, while protecting patient identity and confidentiality.

In order to protect their identity, patients are assigned an arbitrary code connecting their data with identifiers (key coding). The key code can be, for example, a hospital clinical trial code, and can be decoded only by the hospital and investigator if additional information is needed, such as might be required during an epidemiological investigation of an event. Clinical centres and investigators are identified by name.

To achieve effectiveness in recognition of health risks, the database has been designed to collect indexed information using controlled vocabulary and computer-assisted coding software. It is designed specifically to identify common exposures.

In summary, the database collects the following:

1- Registration information on xenotransplantation product recipients, including all related procedures, products and source animals, follow-up clinical examinations, adverse health events and clinical outcomes and survival.

2- Facilities and points of contact for those facilities as provided by the IND sponsor. There are four different types of facilities on which data are available: animal source facilities, animal holding facilities, manufacturing facilities and clinical centres.

Thus, registration data records for a xenotransplantation product recipient include the clinical centre performing the procedure, the date of the procedure, the product used, the investigator, the source animal(s), and the animal source facility from which the source animal was procured.

If adverse xenotransplantation-associated events are identified in recipients of xenotransplantation products, the NXD will be used to:

1. Identify and notify other patients who have received similar xenotransplantation products.

2. Identify source animal(s) and herd(s).

3. Locate archived biological samples from the patient(s) and the source animal(s) for testing.

The current system is being designed specifically for clinical trials and not for post-marketing monitoring. The question of how to modify or enhance the system so that it will continue to function well in a post-marketing environment still needs to be resolved.

Thus, the greatest utility of the US database to date is its development of an early set of standards on core data requirements for xenotransplantation surveillance. Yet, as the annual operating cost of the US NXD is forecast at about USD 300 000, such a surveillance approach may appear too costly for many countries; thus, wider diffusion of similar database mechanisms in the near future appears unlikely without corporate willingness to participate in such costs.

Lessons learned during the pilot study of the US National Xenotransplantation Database will be of significant value in developing approaches for effective sharing and comparing of data in xenotransplantation clinical trials worldwide. This is especially the case since US efforts toward development of an NXD require solutions to complex problems and an unprecedented degree of standardisation in the definition of:

1. Core sets of required information.
2. Formats for representation of data.
3. Methods for ensuring data quality.
4. Vocabulary and terminology for shared databases.
5. Mechanisms for data collection and transmission.
6. Reporting requirements.
7. Methods for preserving the confidentiality of patients.

5. Developing a concept framework for international xenotransplantation surveillance

5.1 The need for international xenogeneic infection and disease event surveillance

At present, international xenogeneic infection and disease event surveillance does not exist. Support for its development stems from the realisation that:

- Interest in performing clinical xenotransplantation continues.
- There are inherent infectious disease risks associated with xenotransplantation.
- Past attempts to perform xenotransplantation have not always been accompanied by efforts to prevent, detect or manage possible xenogeneic infection/disease.
- With the potential for worldwide transmission of xenogeneic infection or disease, countries engaged in xenotransplantation as well as those not wishing to do so will be at risk of xenogeneic infection/disease exposure.

The development of and participation in international xenogeneic infection/disease event surveillance will assist countries in managing potential risk, whether the risk involved is originating from within their borders or from without.

5.2 General attributes of international surveillance

Three fundamental attributes will be needed for international surveillance:

1- Harmonization of norms for standardising the quality and configuration of surveillance data and information

This should include an internationally agreed xenogeneic infection/disease case definition, and internationally agreed norms for standardising data, information and reporting. (Data derived from different independent national surveillance activities must be comparable and compatible for meaningful international interpretation of event occurrence and importance.) Harmonisation should lead to agreement on what surveillance activities are essential internationally (*e.g.* the detection and reporting of xenogeneic infection or disease events, the collection and analysis of data about the population(s) at risk).

2- Flexibility in the surveillance infrastructure

Infrastructure flexibility is an essential attribute to accommodate the diversity of quality-controlled and valid surveillance approaches found in different countries. The framework chosen for international surveillance should provide a suitable and accessible avenue for encouraging international co-operation and co-ordination; it should benefit from the different perspectives, approaches and possible contributions of its participants. It should permit adjustments and refinements to the xenogeneic infection/disease event case definition, and to surveillance norms and activities, as the understanding of xenogeneic infection/disease risk evolves and the capability to diagnose and detect infection and disease events improves.

3- The ability to balance appropriately the timely detection and reporting of international events with accuracy in detection and reporting

Furthermore, to be effective, international surveillance has to be more than just the compilation of statistics. Its overall goal must be to trigger responses to public health events of international significance. This can be accomplished through the generation of timely validated data on xenogeneic infection/disease events and xenotransplantation performance worldwide; the analysis and transformation of internationally relevant data into meaningful information; and, very importantly, the communication of information to decision makers in different countries.

5.3 A network as a possible framework for international xenotransplantation surveillance

A network for international xenogeneic infection/disease event surveillance can incorporate all three of the surveillance attributes mentioned above.

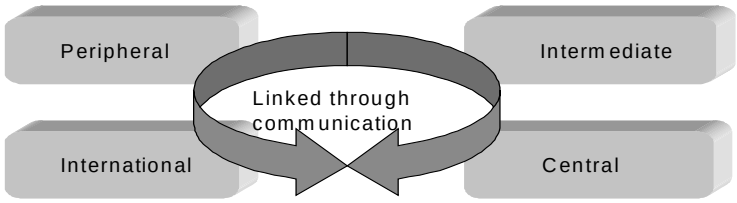
Furthermore, a network composed of national and other relevant members, connected by channels of communication, can:

- Be tailored to reflect the various biologic behaviours and characteristics of the spectrum of potential xenogeneic infectious agents.
- Synergise with already existing successful surveillance systems based on a network configuration.
- Derive strength from the diversity of perspectives of its contributing members.

– Promote international surveillance credibility by providing a neutral, central platform for information dissemination both to national authorities and to the interested public.

In general, four administrative levels could be considered for a network: peripheral, intermediate, central or country-wide, and international. As many countries already have a public health framework based on community (peripheral), region or state (intermediate), and country-wide (central) administrative levels, the same format could be used for xenogeneic infection/disease event surveillance systems. This could allow some synergy with other surveillance activities and help avoid unnecessary duplication. An international co-ordinating level could then be added to connect and complement the country-based systems.

Figure 1. Basic outline of a network



5.3.1 The peripheral network level

This level is the network's most proximal point to xenotransplantation product production and use, and therefore to xenogeneic infection/disease risk. Its principle purpose would be to detect and report the occurrence of xenogeneic infection and/or disease.

Box 1. Proposed members and activities of the peripheral network level

Members of the peripheral level could include:

– Primary healthcare providers.

– Local or community health services.

– Xenotransplantation centres or programmes.

– Laboratories performing diagnostic testing.

– Other public or private interested partners as appropriate.

Its activities could encompass:

– The generation of data on xenogeneic infection/disease event occurrences and populations at risk.

– Regular and emergency communication with other network levels.

– Receipt and use of feedback on data quality and usefulness, and on how the peripheral-level network members might improve or refine their surveillance activities.

5.3.2 The intermediate network level

Depending on the public health, social and administrative structure of a country, this level may play a significant role in the network (for example in decentralised administrative units where public health functions are performed by state or provincial governments, or when there is a large xenotransplantation programme conducting activities in multiple centres at different locations). The intermediate level may, however, have a lesser role in countries where most public health functions are carried out by the central government only. The main function of this network level should be to facilitate the work of the network's peripheral and central levels.

Box 2. Proposed members and activities of the intermediate network level

Members of the peripheral level could include:

- Multi-centre xenotransplantation programmes.
- Diagnostic laboratories serving more than one xenotransplantation centre.
- District, provincial or state public health services.
- Associations among xenotransplantation centres or programmes.
- Other public or private interested partners as appropriate.

The principle activities of the intermediate level could encompass the:

- Aggregation and analysis of data generated by the peripheral level.
- Performance of peripheral-level quality assurance oversight.
- Provision of laboratory services not available at the peripheral level.
- Provision of feedback to the peripheral level on xenogeneic infection/disease event information.
- Efforts to improve the speed with which information on suspected/confirmed occurrences of xenogeneic infection/disease events is shared.

5.3.3 The central or country-wide network level

Ultimate authority and responsibility for a country's xenogeneic infection/disease event surveillance system would lie at the central network level, whose main purpose would be to analyse and disseminate data, and provide co-ordination and oversight for all xenotransplantation surveillance activities in a country. The central level, however, would not perform the same function as a country's xenotransplantation regulatory authority – a separate body.

The two bodies would be very complementary in their functions, and in some cases a number of individuals or authorities could participate in both.

Box 3. Proposed members and activities of the country-wide network level

Members of the country-wide level could include:

- A country's authorities or other bodies appointed or accredited for national xenogeneic infection/disease event surveillance.
- Other organisations with recognised authority to conduct and/or oversee xenogeneic infection/disease event surveillance.

Activities could include:

- Determining what xenotransplantation performance and xenogeneic infection/disease event data should be collected or otherwise be available for surveillance purposes.
- Assuring that such data and records are maintained and accessible.
- Assuring that xenotransplantation performance and xenogeneic infection/disease event data are properly analysed and interpreted into useful information.
- Assuring that the resulting information is communicated to the most appropriate decision makers for use.
- Verifying xenogeneic infection/disease event occurrence(s).
- Supporting other levels by providing access to services not otherwise available at those levels.
- Providing and supporting network feedback and capacity building.
- Reporting xenotransplantation performance and xenogeneic infection/disease event information to the international network co-ordinator.
- Liasing with the international network co-ordinator on internationally significant xenogeneic infection/disease events.
- If necessary, participating in co-ordinated xenogeneic infection/disease responses to events of international magnitude.

5.3.4 The international network level

This level would serve as overall co-ordinator of an international xenogeneic infection/disease event surveillance network. It can take the form of either a single lead organisation or a consortium of network members with administrative functions under the direction of a central secretariat. No matter what its form, however, it must act to maximise worldwide public health benefit from xenogeneic infection/disease event surveillance activities. Different national and international regulatory and administrative norms would determine the conditions under which participation in the international level is possible.

Box 4. Proposed members and activities of the international network level

Members at this level could include:

- A country's authority or administrative body responsible for xenogenic infection/disease event surveillance (central level members).
- Public or private organisations with significant activity in international xenogeneic infection/disease event surveillance, and which can add value to the operation and functioning of the network.
- Others as appropriate.

Activities that should be conducted at the international network level include:

- Promoting the use of internationally accepted norms for surveillance data, information and reporting.
- Facilitating clear and open channels of communication for reporting.
- Registering reports of xenotransplantation performance and xenogeneic infection/disease event occurrences.
- Verifying, analysing and interpreting received information about xenogeneic infection/disease events.
- Facilitating event notification to countries and network members.
- Encouraging national and international capacity building.
- Providing feedback to members on xenotransplantation performance, xenogeneic infection/disease events and network activities.
- If necessary, guiding and co-ordinating activities in response to events of international magnitude.

6. Results from Working Group discussions on international xenotransplantation surveillance

Three Working Groups were formed to answer questions that grew out of the round-table discussions. Included below are the joint summary conclusions from the Working Group discussions.

Do we need international surveillance for xenotransplantation?

The overwhelming view of participants at the Working Groups was that the establishment of a mechanism for international surveillance to detect any possible case of xenogeneic infection/disease with potential for transmission is needed. It was agreed that such a mechanism should be based on a communication network of designated national facilities/contacts, and that it should aim at:

- Encouraging standardisation of definitions and methodologies used for xenotransplantation-associated surveillance.
- The identification and early warning of xenotransplantation-associated adverse events of international public health importance.
- Enabling the detection of rare adverse events not readily detected by national surveillance mechanisms.
- Sharing essential information for assessment and promotion on xenotransplantation product recipient safety and health.

What information is needed for international xenotransplantation surveillance?

The participants agreed that an internationally accepted and used case definition for a xenotransplantation-associated infectious disease was the starting point for determining what information was essential for conducting international surveillance. It was felt that any case definition should include an internationally agreed statement on what constitutes a xenotransplantation product. The case definition should unambiguously describe what a xenotransplantation-associated adverse event is, and also permit the incorporation of new information about its nature and expression as clinical experience with xenotransplantion-associated infectious diseases is gained.

Once an internationally agreed case definition is developed, a determination can be made as to what information will be needed to successfully conduct international surveillance. In general, it was felt that the essential information would contain data on:

- The numbers and types of xenotransplantation procedures being performed.
- The number and types of adverse events detected following xenotransplantation.
- The identity of the xenozoonotic agent (confirmed or suspected).
- The laboratory criteria used to make the diagnosis.

Sharing of information on potential serious adverse events in xenotransplantation product recipients and close contacts is also considered useful, but this information should always be handled in such a way as to protect the confidentiality and rights of the individuals from whom this information is derived.

Which individuals should be surveyed?

It was agreed that the UKXIRA draft document on "Infection surveillance post-xenotransplantation" provided useful guidance with regard to which individuals should be the subject of xenotransplantation-associated infectious disease surveillance. In this document, the population under surveillance is defined and includes recipients, donors, healthcare workers, caregivers, and source animals. The Consultation participants, however, emphasised that the role of any international surveillance system should be to report transmission of xenogeneic infections from recipients to their contacts, and not to routinely collect information on the contacts themselves in the absence of identification or notification of such transmission.

How should direct exposure to a xenotransplantation product be defined?

All groups agreed that addressing this question required consensus on a definition for xenotransplantation products and processes. The importance of being inclusive rather than exclusive in defining xenotransplantation products and processes was stressed. There was overall agreement that the definition adopted by the US PHS would be a good starting point. (A proposal would be: *Exposure either by implantation, infusion, or ex vivo perfusion to either (a) nonhuman animal cells, tissues or organs, or (b) human cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs – including exposure to these directly or encased in bioengineered products*.)

What should be the time frame for data collection?

There was consensus that, based on current scientific understanding, surveillance of people who have been exposed, regardless of the fate of xenotransplantation technology, would need to be long-term, and continue for decades as long as the technology is applied or the patients are alive. However, time frames and intervals for data collection would also need to be re-evaluated periodically.

Should xenotransplantation registries be operated by industry or government?

It was proposed that it will be difficult to achieve openness in sharing data across geopolitical boundaries. Transparency may be best achieved if national public health authorities take direct action by, for example, setting standards and norms on data collection, storage and access. Participation and co-operation with industry is indispensable, as most clinical trials are run by the private sector.

Is an international registry necessary? Should/could the xenotransplantation registry be linked internationally?

The general consensus was that internationally, a registry is not necessary, provided essential information can be shared and is compatible between sources. All groups felt that it would be best to develop an international system through linkage of national registries or surveillance systems. Attempts to develop a *de novo* international xenotransplantation registry would most likely fail. It was also agreed that it would be unwise to attempt to develop new registry methodologies. Instead, the use of existing standard vocabularies should be considered for reporting adverse events.

7. Consultation conclusions and recommendations

The range and depth of the discussions conducted during the Consultation reflected the complexity of both the infectious disease issues associated with xenotransplantation practice and the nature of infectious disease surveillance in general. These discussions highlighted several points.

Identifying an appropriate case definition for xenogeneic infectious diseases is the critical first step toward designing a surveillance system. *The challenge faced in xenotransplantation will be to structure a case definition which encompasses specifically identifiable signs and symptoms known to be associated with xenogeneic infectious disease, yet also encourage the thoughtful search for seemingly unexpected but associated events.* This duality will not be easily reconciled. Furthermore, the desire to identify as yet unknown infectious disease consequences of xenotransplantation will tend to factor complexity into the surveillance system framework. A complex and intricate system designed to ideally detect all conceivable eventualities will be difficult to implement, both at a national level and internationally. It could hinder the necessary capacity of a system to rapidly detect and respond to a xenogeneic infectious disease event, should it occur. Thus, achieving both the ability to identify and to respond rapidly and effectively to a xenogeneic infectious disease event, especially one with a previously unrecognised syndrome, represents a substantial but unavoidable challenge. Also, designing a streamlined and agile xenogeneic infectious disease surveillance system is complicated by both the absence of any organised surveillance network for allotransplantation and the diversity of surveillance approaches now under consideration. This diversity is the result of quite valid and reasonable attempts to address the various public health, scientific, economic, social, legal and ethical issues associated with xenotransplantation. It also stems from the different individual and organisational languages and cultural perspectives applied to understanding and working with these disciplines. The harnessing of this diversity into a productive surveillance application will require a harmonisation of vocabularies, norms and objectives.

The Consultation reviewed how many countries are currently trying to address the potential risks and benefits of xenotransplantation, as well as their plans for specific policies, regulations, guidelines, standards and uses of national expert advisory bodies. Such information is available on the OECD Website http://www.oecd.org/dsti/sti/s_t/biotech/xenosite/country.htm. A common concern was the potential introduction of xenogeneic pathogens into a community, and in particular the uncertainty of predicting such an occurrence. *Thus, current national frameworks have incorporated very high benchmarks for safety – some countries have initiated moratoria, some have limited xenotransplantation to laboratory-based research, others to clinical trials only*.

Most countries cited the "Precautionary Principle" as the basis for their action, but different meanings have been applied to this "principle", a fact that is having a profound influence on the approaches taken. In its most basic form, the Consultation participants thought that the principle implies that one should not wait until a risk is confirmed before taking action. *Thus, in light of the number of xenotransplantation clinical trials currently under way, a proactive engagement is recommended*. This might entail the development of a new paradigm for surveillance, *i.e.* not to rely solely on clinical syndromes to drive surveillance but to actively search for unknown or unanticipated agents in the absence of recognisable clinical syndromes. Thus, consideration was given to selecting laboratory testing methods that feature the use of generic markers for categories of infectious agents in addition to or in preference to laboratory methods based on detecting specific agents. The advantage of these less specific assays is that they may detect variants for which standard assays may not be adequately sensitive or available, and can be used to look for agents not yet recognised. In many cases, however, these tests still require standardisation and validation, and may be costly because of the equipment, specialised reagents and skilled staff required. *Thus, an effort towards sharing and co-operation on expertise and laboratory practices will need to be integrated in both national and international xenotransplantation surveillance schemes*. Collaboration between public and private laboratories will also be necessary to sustain and enable such an approach. The possibility of designating – on a regional base – accredited excellence centres to run such tests was considered.

Overall, participants emphasised that in attempting to design a surveillance system, it is important to recognise that surveillance is not an end in itself. Surveillance is a tool intended to deliver an early alert to allow response. It allows and requires decision making on the basis of imperfect information. In the case of xenotransplantation, simple systems that allow early judgements may be preferable to complex systems that aim to collect as much information as possible but in doing so would delay early alert and response. However, it was also acknowledged that a xenotransplantation surveillance system should be as powerful as possible and that no existing surveillance system is so sensitive as to detect rare events in the absence of any knowledge of the normal background or threshold of disease events. *Lessons learned from rare neurologic diseases, such as Kawasaki syndrome, suggest that in early xenotransplantation trials clinicians might need to report regularly not only what they have seen, but also what they have* ***not seen***. In that way, over time a useful picture of background incidence will emerge.

Thus, countries should be encouraged to carefully scrutinise and compare xenotransplantation protocols in order to verify efficacy and to indicate areas for future research.

Countries should also be encouraged to:

- *Establish national registries to address surveillance issues for individual and public safety.*
- *Designate national xenotransplantation surveillance facilities.*
- *Enable linkage of national registries to corporate and international xenotransplantation registries.*
- *Adopt internationally agreed criteria for testing and reporting to ensure comparability of data.*

- *Facilitate free exchange of information among key stakeholders while protecting the confidentiality of individual patients and investigators.*
- *Provide the means by which non-confidential generic information for patient and public education could be easily derived and automatically updated.*
- *Design systems flexible enough to accommodate changes in:*
  - *The reporting of markers of infection (new diagnostic assays, recognition of markers learned or suspected to indicate infection non-specifically (e.g. CD4 / CD8 ratio change in AIDS).*
  - *The population under surveillance (e.g. documentation of transmission from recipient to contact leading to decision to also survey contacts).*

Overall, workshop participants felt that it would be best to develop an international system through linkage of national registries or surveillance systems. However, attempts to develop a *de novo* international surveillance system would most likely fail.

The Consultation led to agreement on the overriding need to strengthen communication between the scientific and policy making communities, and among public health officials, the private sector and the public. For surveillance to be effective it must be acceptable – to sponsors, practitioners and the broader public, as well as to governing bodies. Programmes to inform and educate the broader public are thus of critical importance and should be carefully planned together with those that will be primarily concerned with the implementation of surveillance schemes. Lack of acceptability results in delays in reporting and limited public dissemination of the information gained through surveillance due to political concerns. In addition, effectiveness requires regular feedback; adequate internal and external quality controls; continuing education and regular evaluation, both on how to report and on how to use feedback data in meaningful ways; and incentives and co-operation for reporting, as well as guidance on quality of reporting.

Overall, participants recommended calling broadly for the dedication of resources to support ongoing clinical research and research on identification of additional infectious agents of concern; developing an expanded array of diagnostic assays; and identifying generic markers of infection that would enable prospective data collection for surveillance. The WHO in co-operation with the OECD and other relevant international bodies (*e.g.* Council of Europe) was invited to take a leadership role in facilitating the development of internationally agreed norms for testing and reporting, and of an effective xenogeneic infectious disease surveillance network. Common frameworks could promote international information sharing and co-operation, and could provide a mechanism for facilitating the balance between the need to protect public health and the need to respect human rights and dignity worldwide. Synergies could be achieved by tapping into already existing resources. For example, the standardised vocabulary developed in MedDRA could be used as the language for detection and reporting; the GPHIN system could be used for the rapid dissemination of information.

Finally, a xenogeneic infectious disease surveillance network could be managed either by a single lead organisation or a consortium of network members with administrative functions under the supervision of a central secretariat. Regardless of its format, it will be essential that the network be owned by all its members, who would share its benefits as well as its costs and responsibilities.

APPENDIX I

PROGRAMME AND LIST OF PARTICIPANTS

JOINT WHO/OECD CONSULTATION
ON XENOTRANSPLANTATION SURVEILLANCE[17]
4 - 6 OCTOBER, 2000
OECD, PARIS

PROGRAMME

Meeting Attendees:

(By invitation only): policy makers, medical researchers, clinicians, epidemiologists, *etc*.

Objectives:

At the 1997 WHO Consultation, the Canadian Forum 1997, the OECD New York '98 workshop, and the UKXIRA '99 meeting, it was suggested that a first step towards global co-operation on xenotransplantation surveillance could be furthered through the development of internationally agreed guidance on reporting norms, and use of compatible information technology.

This consultation addresses this suggestion by:

- Facilitating national and international policy considerations on the desirability, purpose, structures and functions of xenotransplantation surveillance, taking into account the different applications of xenotransplantation.
- Reviewing current surveillance systems as operational models for the design of xenotransplantation surveillance.
- Considering what technical information and logistic elements might be useful in support of effective international xenogeneic infection/disease surveillance.

17. The Canadian Government's support to make this consultation possible is gratefully acknowledged.

DAY 1

Welcome and introduction: Dr. F. Meslin, WHO; Dr. E. Ronchi, OECD

Key-note Introduction:

Xenogeneic infection/disease surveillance: What are we looking for? How important is it? What do we do when we find it?

Speaker: Dr. J. Fishman, Infectious Disease Division,
Massachusetts General Hospital, United States

Session 1 : ***Existing surveillance models: examples of current forms***

Moderator: Dr. P. Hunter, Chester Public Health Laboratory Service, United Kingdom

A. ***The conduct of infectious disease surveillance in the clinical setting***

Speaker: Dr. A. Leelarasamee, Division of Infectious Diseases
Faculty of Medicine, Siriraj Hospital, Thailand

B. ***Pharmacovigilance: an international perspective***

Speaker: Dr. F. Rinaudo, EMEA

C. ***Pharmacovigilance in xenotransplantation studies - definitions and standards for expedited reporting***

Speaker: Dr. L. Thomas, Novartis-Imutran

Session 2: ***Existing surveillance models: disease-specific systems***

A. ***Example of national level infectious disease surveillance system***

B. ***Example of an infectious disease specific international surveillance system***

Speaker: Dr. A. Rushdy, United Kingdom, EC-DG-Health and Consumer Protection

Session 3: ***Xenogeneic infection/disease surveillance models***

A. ***Industry surveillance and contigency plans in xenotransplantation/xenografting clinical trials***

Speakers: Dr. S. Stewart, Genzyme
Dr. Z. Pitkin, Circe Biomedical

B. ***The point of view of the virologists: questions for the roundtable discussion***

Speakers: Dr. J. Schupbach, Swiss National Center for Retroviruses, Switzerland

Roundtable and audience discussion: ***What aspects of these surveillance systems might be applicable to xenotransplantation infection/disease surveillance?***

Moderator: Dr. R. Manez, Juan Canajelo Medical Center, Spain

Day 2

Session 4: ***What attributes are needed in xenotransplantation surveillance?***

Moderators: Prof. G. Griffin, UKXIRA, United Kingdom; Dr. E. Ronchi, OECD

A. ***The specialized needs of early detection and response to infection and disease events: Investigative surveillance***

Speaker: Prof. J. Weinberg, Provice Chancellor (Research) City University, London, United Kingdom

B. ***Global Public Health Intelligence Network (GPHIN): a system for the rapid communication of surveillance information***

Speaker: Dr. Rudi Nowak, WHO

C. ***Xenotransplantation surveillance, databases, registries and archives: country reports***

Speakers: Dr. R. Manez, Juan Canajelo Medical Center, Spain
Dr. E. Bloom, FDA, United States
Dr. M. Bouvier d'Yvoire, *Etablissement français des Greffes*, France
Prof. G. Griffin, UKXIRA, United Kingdom

Mr. A. La Prairie, Health Canada, Canada
Dr. J. Schupbach, Swiss National Center for Retroviruses, Switzerland
Dr. M. Kenter, CCMO, The Netherlands
Dr. K. Cichutek, Paul-Ehrlich Institute, Germany
Dr. A. Sargentini, *Istituto Superiore di Sanità*, Italy
Dr. A. Tibell, Huddinge University Hospital, Sweden
Dr. F. Cantarovich, Argentina
Dr. P. O'Connell, Westmead Hospital, Australia

Session 5: ***Designs for surveillance effectiveness***

Moderator: Dr. F. Meslin, WHO

A. ***Databases for xenotransplantation surveillance: concepts and designs***

Speaker: Dr. J. Foss, FDA, United States

B. ***Ethical considerations in xenotransplantation surveillance***

Speaker: Dr. A. Daar, Sultan Qaboos University, Oman

C. ***WHO presentation of a starting point for discussion of a framework for international xenogeneic infection/disease event surveillance.***

Speaker: Dr. C. Witt, WHO

Roundtable and audience discussion : ***What are the core attributes of effective surveillance and which would/should transcend national borders?***

Moderator: Dr. L. Chapman, Centers for Disease Control and Prevention, United States

Session 6

Working Group Break-Out for debate on key issues identified during the round table discussions

Day 3

Report from Working Groups - Final considerations

Rapporteur: Dr. L. Chapman, Centers for Disease Control and Prevention, United States

Chairs' Summary of Main Points - Closing of meeting

OECD/WHO CONSULTATION ON XENOTRANSPLANTATION AND SURVEILLANCE
4-6 October 2000

LIST OF PARTICIPANTS

CHAIRS

Mr. André LA PRAIRIE
Policy Analyst
Health Canada
11 Holland Ave.
2nd Floor
Postal Locator 3002B2
Ottawa, ONT K1A 1B6
Canada

Mr. Amorn LEELARASAMEE
Division of Infectious Disease, Faculty of Medicine,
Siriraj Hospital
Bangkok
Thailand

RAPPORTEUR

Dr. Louisa CHAPMAN
Centers for Disease Control and Prevention
1600 Clifton Rd. N.E.
Atlanta, GA 30333
United States

MODERATORS

Dr. Louisa CHAPMAN
Centers for Disease Control and Prevention
1600 Clifton Rd. N.E.
Atlanta, GA 30333
United States

Prof. George GRIFFIN
St. George's Hospital Medical School
Cranmer Terrace
London SW17ORE
United Kingdom

Prof. Paul HUNTER
Director, Consultant, Medical Microbiologist and Epidemiologist
Chester Public Health Laboratory Service
Countess of Chester Health Park
Liverpool Road
Chester CH2 1UL
United Kingdom

Dr. Rafael MANEZ
Director of Transplantation Medicine and Xenotransplantation
Juan Canalejo Medical Center
Xubias de Arriba 84
15006 La Coruna
Spain

Dr. F. MESLIN
Chief, Zoonosis Unit
Division of Emerging and other Communicable Diseases
Surveillance and Control (EMC)
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Dr. Elettra RONCHI
Co-ordinator, Health and Biotechnology Activities
OECD
2, rue André Pascal
75775 Paris Cedex 16
France

SPEAKERS

Dr. Annick BIGORIE
Etablissement français des Greffes
Département Médical et Scientifique
Pôle "Sécurité - Qualité"
5 rue Lacuée
75012 Paris
France

Dr. Eda BLOOM
Chief, Laboratory of Cellular Immunology
Chair, Xenotransplantation Action Plan
Division of Cellular and Gene Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852
United States

Dr. Michel BOUVIER d'YVOIRE
Etablissement français des Greffes
Département Médical et Scientifique
Pôle "Stratégie - Recherche - Développement"
5 rue Lacuée
75012 Paris
France

Dr. Felix CANTAROVICH
Former National Director of the CUCAI (Organ Sharing National Organisation of Argentina)
14, rue Fantin Latour
75016 Paris
France

Prof. Dr. Klaus CICHUTEK
Head, Department of Medical Biotechnology
Paul-Ehrlich-Institut
Federal Agency for Sera and Vaccines
Paul-Ehrlich-Str. 51-59
63225 Langen
Germany

Dr. A. DAAR
Chairman
Sultan Qaboos University
P.O.Box 35
123 Al-Khod
Oman

Dr. Jay A. FISHMAN
Associate Professor of Medicine
Harvard Medical School
Clinical Director
Transplant Infectious Diseases Programme
Massachusetts General Hospital
32 Fruit Street
Boston, MA 02114
United States

Mr. Jim FOSS
Stellar Systems, L.L.C.
8245 Boone Boulevard, Suite 708
Vienna, VA 22182
United States

Prof. George GRIFFIN
St. George's Hospital Medical School
Cranmer Terrace
London SW17ORE
United Kingdom

Dr. Marcel KENTER
Executive Director
CCMO, Central Committee for Research Involving Human Subjects
P.O. Box 16052
2500 BB The Hague
The Netherlands

Mr. André LA PRAIRIE
Policy Analyst
Health Canada
11 Holland Ave.
2nd Floor
Postal Locator 3002B2
Ottawa, ONT K1A 1B6
Canada

Mr. Amorn LEELARASAMEE
Division of Infectious Disease, Faculty of Medicine,
Siriraj Hospital
Bangkok
Thailand

Dr. Rafael MANEZ
Director of Transplantation Medicine and
Xenotransplantation
Juan Canalejo Medical Center
Xubias de Arriba 84
15006 La Coruna
Spain

Dr. Rudi NOWAK
Integrated Surveillance and Response
Department of Communicable Disease Surveillance
and Response
World Health Organization (WHO)
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Dr. Philip O'CONNELL
Department of Nephrology, Westmead Hospital
Westmead, NSW 2145
Australia

Dr. Zorina PITKIN
Vice President, Regulatory and QA/QC
Circe Biomedical
99 Hayden Avenue
Lexington, MA 02173
United States

Dr. Franco RINAUDO
EC Joint Research Centre
7 Westferry Circus
Canary Wharf
London 314 4HB
United Kingdom

Dr. Amal RUSHDY
Department of Health
Room 420
Wellington House
133-155 Waterloo Road
London
SE1 8UG
United Kingdom

Prof. Aurelia SARGENTINI
Director, Laboratory of Biomedical Engineering
Instituto Superiore di Sanità
Viale Regina Elena, 299
00161 Rome
Italy

Dr. Jorg SCHUPBACH, M.D.
Director
Swiss National Center for Retroviruses
University of Zurich
Gloriastrasse 30
CH-8028 Zurich
Switzerland

Ms. Susan STEWART
Sr. Director, Regulatory Affairs
Genzyme Corporation
Diacrin/Genzyme LLC
1 Kendal Square
Building 1400
Cambridge, MA 02139
United States

Ms. Lucy THOMAS
Imutran Ltd.
Raglan House
159 High St.
Aldershot
Hants GU11 1TT
United Kingdom

Dr. Annika TIBELL
Associate professor of Transplantation Surgery
Department of Transplantation Surgery
Huddinge University Hospital
Karolinska Institute
S141 86 Stockholm
Sweden

Prof. J. WEINBERG
Provice Chancellor (Research)
City University London
United Kingdom

Dr. Clara J. WITT
Animal and Food Related Public Health Risks
Temporary Adviser
Department of Communicable Disease Surveillance
and Response
World Health Organization (WHO)
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

PARTICIPANTS

Ms. Silvia ARDOY
Former Argentina Judge in charge of criminal investigation
Legal Advisor UNDP
14 Rue Fontaine Latour
Paris 75016
France

Dr. Ulrich BEUTNER
Experimental Transplantation Immunology (ETI)
Department of Surgery
University of Wuerzburg
Josef-Schneider-Strasse 2
D-97080 Wuerzburg
Germany

Dr. José AMATE BLANCO
Agencia de Evaluacion de Tecnologias Sanitarias
Instituto de Salud Carlos III
Ministerio de Sanidad y Consumo
C/ Sinesio Delgado 6 (Pabellon 3)
28029 Madrid
Spain

Dr. Phil BROWN
Regulatory Affairs Manager
Genzyme BV
Gooimeer 10
1411 DD Naarden
The Netherlands

Dr. Anne CASTOT
Responsable du département des vigilances
Agence française de sécurité sanitaire
des produits de santé (AFSSAPS)
143/147, Bd Anatole France
93285 Cedex Saint Denis
France

Dr. Rebecca CINTRON
Senior Director, Pharmacovigilance
Genzyme Corporation
Cambridge, MA 02139
United States

Dr. Wim H. DE JONG
RIVM (National Institute of Public Health and the Environment)
Laboratory of Pathology and Immunobiology
P.O. Box 1
3720 BA Bilthoven
The Netherlands

Dr. Ezzat FARZAD
Division of Blood-Borne Pathogens
Centre for Infectious Disease Prevention and Control
Population and Public Health Branch
Health Canada
Room 1438 LCDC Building
Postal Locator: 0601E2
Tunney's Pasture
Ottawa, Ontario K1A 0L2
Canada

Dr. Giovanni FRACCHIA
Principal Administrator
Health and Consumer Protection
Management Scientific Committees I
European Commission
Rue Belliard 232 6/63
1040 Brussels
Belgium

Dr. Clara FRONTALI
Research Director
Istituto Superiore di Sanità
Viale Regina Elena 229
00161 Rome
Italy

Dr. Karoline DORSCH-HÄSLER
Swiss Agency for the Environment, Forests and Landscape
CH-3003 Bern
Switzerland

Mr. Martin HOUGHTON
UKXIRA Secretariat
Department of Health
315 Wellington House
133-155 Waterloo Road
London
SE1 8UG
United Kingdom

Ms. Gerda HUISMAN
Ministry of Health, Welfare and Sport
Directorate for Drugs and Medical Devices
P.O. Box 20350
NL-2500 The Hague
The Netherlands

Prof. Ejvind KEMP
Herlev Hospital, Institute of Pathology
2730 Hevlev
Denmark

Dr. Cornelia KUNZ
Federal Office of Public Health
Département fédéral de l'Intérieur
CH-3003 Bern
Switzerland

Dr. Marian LADEROUTE
Blood Zoonotics Unit
Bloodborne Pathogens Division
Bureau of Infectious Diseases
Health Canada, CIDPC, LCDC #6, Room 1420
AL 060 1E2
Tunney's Pasture
Ottawa, ONT K1A 0L2
Canada

Patrick LAMBRECHT
Flemish Interuniversity Institute
of Biothechnology (VIB)
Pleinlaan 2
1050 Brussels
Belgium

Ms. Sophie LUCAS
Département de l'évaluation des produits biologiques
Agence française de sécurité sanitaire
des produits de santé (AFSSAPS)
143/147, Bd Anatole France
93285 Cedex Saint Denis
France

Dr. Line MATTHIESSEN
European Commission - Research DG-B-II-3
200 rue de la Loi
1049 Brussels
Belgium

Dr. Khazal PARADIS
Novartis Pharma AG / Imutran Ltd.
PO Box 399
Cambridge CB2 2YP
United Kingdom

Dr. Jim PEARSON
Office international de épizooties
Département scientifique et technique
12 rue de Prony
75017 Paris
France

Ms. Isabelle SAINTE MARIE
Département de l'évaluation des produits biologiques
Agence française de sécurité sanitaire
des produits de santé (AFSSAPS)
143/147, Bd Anatole France
93285 Cedex Saint Denis
France

Dr. Rudolf SCHUSTER
Ref. 1x19b
Ministry of Social Affairs and Generations
Radetzkystrasse 2
A-1031 Vienna
Austria

Prof. Dr. Karin ULRICHS
Experimental Transplantation Immunology (ETI)
University Hospital of Surgery
Josef-Schneider-Strasse 2
D-97080 Wuerzburg
Germany

Ms. Pierrette ZORZI MORRE
Responsable du Départment de l'Evaluation
des Produits biologiques
Agence française de sécurité sanitaire
des produits de santé (AFSSAPS)
143/147, Bd Anatole France
93285 Cedex Saint Denis
France

Mr. Keiji TAKEBAYASHI
Second Secretary
Permanent Delegation of Japan to the OECD
11, avenue Hoche
75008 Paris
France

Dr. Hiroshi YOSHIKURA
Director-General, Research Institute
International Medical Center of Japan
1-21-1 Toyama
Shinjuku-ku
Tokyo 162-8655
Japan

WORLD HEALTH ORGANIZATION

Dr. F. MESLIN
Chief, Zoonosis Unit
Division of Emerging and other Communicable Diseases,
Surveillance and Control (EMC)
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Dr. Rudi NOWAK
Integrated Surveillance and Response
Department of Communicable Disease Surveillance and Response
World Health Organization (WHO)
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Dr. Clara J. WITT
Animal and Food Related Public Health Risks
Temporary Technical Adviser to the World Health Organization (WHO)
Department of Communicable Disease Surveillance and Response
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

OECD SECRETARIAT

Dr. Elettra RONCHI
Co-ordinator, Health and Biotechnology Activities
OECD
2, rue André Pascal
75775 Paris Cedex 16
France

Ms. Alysia RITTER
OECD
2, rue André Pascal
75775 Paris Cedex 16
France

APPENDIX II

PRESS RELEASE

"OECD, WHO Consultation Agrees on the Need for International Xenotransplantation Surveillance"

Xenotransplantation, or the science of transplanting animal cells, tissues and organs to human beings, holds out the prospect of treatments for people with organ failure and other intractable diseases. But it also poses major ethical and public safety issues which still require further study.

In an effort to address some of these issues, scientists, epidemiologists, clinicians, policy makers and representatives of industry met recently at a consultation hosted by the OECD in Paris and organised jointly by the OECD, the World Health Organisation and the Government of Canada. The meeting concluded that there is a need for international surveillance of xenotransplantation activities, and that policy makers should ensure that necessary measures are taken to minimise potential risks to public health.

The consultation brought together some 70 participants from countries currently hosting xenotransplantation clinical trials, engaged in xenotransplantation research and others who have banned the use of the technology but are aware of its global implications. André La Prairie of Health Canada, co-chair of the consultation, and Dr. Louisa Chapman of the United States Centers for Disease Control and Prevention (CDC), who was its rapporteur, outlined the main objectives of international xenotransplantation surveillance as being:

- To detect rapidly and report an infectious disease event, particularly a rare event, should it occur.
- To share information and co-operate.
- To facilitate xenogenic disease event verification and response co-ordination.

Such international monitoring would be intended to operate through pre-established links between countries and other interested parties, rather than through any newly created system. However, it would mean designating national facilities with dedicated resources to collect, analyse and report back international data.

To achieve such objectives, consultation participants agreed, there must be an international consensus on minimal reporting requirements and process. There must also be agreement on the definition of xenotransplantation, which today differs among countries since not all consider xenotransplantation to include cellular transplants from nonhuman animal sources or human body fluids, cells, tissues or organs that have had extracorporeal contact with live nonhuman animal cells or tissues, *e.g*. through bio-artificial organs or assist devices or in cell cultures. Agreement is also needed on case definition including standards on laboratory results or diagnostic assays for international reporting.

Above all, however, the consultation participants agreed that a balance will have to be struck between the potential benefits and the need to protect public health whilst respecting human rights.

For further information please contact Elettra Ronchi: elettra.ronchi@oecd.org, OECD Science and Technology Policy Division.