WHO/HTP/EHT/CPR/2011.01

World Health Organization

Second WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

October 17-19 2011, WHO, Geneva, Switzerland

I. Introduction

The Second WHO International Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials ("Geneva Consultation") convened at WHO headquarters in Geneva, Switzerland, on October 17-19, 2011. Luc Noel welcomed participants, health regulatory authority representatives and internationally recognized experts in xenotransplantation science, law, and ethics from every WHO region, representing 14 Member States. He expressed his thanks to The Transplantation Society (TTS) and the International Xenotransplantation Association (IXA) for their financial support that allowed this consultation to be held.

Emanuele Cozzi, IXA President, pointed out the importance of consensus between health authorities, experts and professionals on the various safety requirements for xenotransplantation clinical practice as demonstrated in Changsha. The need for regular updates justifies the support provided by TTS and IXA, but it is hoped that more conventional sources of funding for normative tasks will be identified in the future.

Ralf Toenjes was elected chairman of the consultation and the Rapporteurs were Richard N. Pierson III, Takaaki Kobayashi, and Keith Wonnacott.

The charge to the consultation was:

1) To review the current status of xenotransplantation science and practice;

2) To determine whether updates to the Changsha Communiqué's guidance to WHO, Member State health regulatory authorities, and study investigators and/or sponsors of xenotransplantation trials are required; and

3) To discuss and refine draft guidance for infectious disease surveillance, prevention, and response appropriate to support various probable clinical xenotransplantation trial scenarios.

II. Current xenotransplantation activity and interim scientific progress.

A. Current progress in xenotransplantation

Significant progress has been reported from preclinical xenotransplantation trials. Multiple groups have achieved sustained normalization of blood glucose coupled with detection of porcine C-peptide in diabetic monkeys and baboons using a variety of immunosuppressive or immune-isolation approaches.

Well documented improvement in Parkinsonian symptoms is frequently observed in immunosuppressed primates following unilateral implantation of genetically modified pig neuronal cells.

Elicited anti-non-Gal antibody can be significantly delayed or, in some instances prevented, using various immunosuppressive protocols that might be clinically relevant. Residual physiologic barriers related to platelet adhesion and coagulation cascade activation by pig

xenografts in primates are well-understood, and several candidate strategies to prevent these phenomena will be tested in the near future.

Islet and neural cell transplantation and perhaps ex vivo liver perfusion (as a bridge to transplant or recovery) are candidate pig-to-human xenograft applications that appear most likely to first reach the clinic, assuming that the Changsha criteria for preclinical evidence of efficacy and safety are met.

B. Regulated xenotransplantation clinical trials

One regulated clinical trial of intra-peritoneal alginate-encapsulated porcine islets in non-immunosuppressed recipients is under way in New Zealand. To date no safety concerns have been reported in 14 encapsulated islet recipients (IPITA abstract 528 -Islets xenotransplantation: New Zealand experience - Olga Garkavenko, Robert Elliott).

The New Zealand regulatory approval and oversight mechanism is thought to be comprehensive. Non-peer-reviewed interim corporate reports do not yet demonstrate clear evidence of efficacy.

No other regulated xenotransplantation trials are currently known to be in progress.

C. Unregulated xenotransplantation clinical trials

Unregulated xenotransplantation continues to be advertised and performed in multiple jurisdictions in contravention of the fifty-seventh World Health Assembly Resolution **WHA57.18** (Annex 1) urging Member States "to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place". These trials are ignoring the requirements expressed in the Changsha Communiqué (Annex 2) and run contrary to the spirit and letter of most guidance documents governing xenotransplantation clinical trials which require regulatory oversight, microbiologic testing, and archived sample repositories for such activities (examples in Annex 3).

To date, no credible evidence of efficacy has been reported for recipients of unregulated living xenograft products. No specific health risks or suspicious pandemic or epidemic syndromes have been detected in association with these xenotransplantation activities, or been reported from the jurisdictions where they are known to be occurring.

However lack of specific surveillance or monitoring activities prevents definitive ascertainment of known or unknown risks that might be associated with unregulated administration of living xenogeneic cells or tissues to humans. Absence of relevant data prevents confidence in the consensus interim conclusion that the risk of symptomatic or asymptomatic contagious infection from current and historical xenotransplantation activities appears to be low.

III. Infectious Disease in Xenotransplantation

Participants reviewed issues associated to the infectious risks of xenotransplantation on the basis of a background paper prepared by Jay A. Fishman, Linda Scobie, and Yasuhiro Takeuchi and shared with participants before the meeting (Annex 3).

This paper was prepared for the Consultation. It proposes general recommendations in the light of progress in knowledge of infectious risks and laboratory investigations in the last years.

The group reviewed issues in light of discussions in breakout groups on the three following themes:

-1) Scenario and proposed response to anticipate the infectious risk that might arise as a consequence of xenograft activities;

-2) Optimizing and standardizing testing and identification of xenotransplantation-associated infection;

-3) Revisiting and prioritizing essential pre-requisites for clinical trials.

The following items were consequently discussed in plenary.

A. Progress with Porcine Endogenous Retroviruses (PERV)

Demonstration that porcine endogenous retrovirus (PERV) can infect human cells raised concerns that this virus might cause disease in a human recipient of a porcine xenograft, and then spread to close contacts, or to the general population.

Considerable additional interim evidence now suggests that:

- Infection of human cells with PERV occurs only under unusual circumstances, and PERV appears to require permissive cell types to propagate.

- Productive PERV infection has not been demonstrated in non-human primates or in human recipients of porcine cells or organs even in the context of intensive recipient immunosuppression in preclinical models. The source pigs for these studies are of undefined PERV phenotypes.

- Strategies to diagnose PERV in the recipient of an organ or cell xenograft have been developed and include both serologic and molecular assays, some of which are useful to detect PERV replication. These assays have the capacity to detect productive infection, should that occur, and to help manage risk for subjects, close contacts, and the public.

- There are also protective strategies, including antiviral agents, which are predicted to prove useful to prevent or manage foreseeable PERV infection scenarios.

- Absence of detection of PERV C or PERV C isotype in a pig xenograft source animal is preferable in principle. Donor and recipient PERV surveillance is mandated, with specific strategy dependent on pig PERV status. Current guidance (e.g. FDA) does not exclude PERV C+ pig source animals, but a positive result must trigger active monitoring.

B. Other relevant known and currently unknown infectious agents in porcine xenotransplantation

Other known infectious agents that may pose a risk to human recipients of pig xenografts are better understood. Most known potential pathogens have been excluded from several pig colonies currently being used for preclinical xenotransplantation research.

Assays exist for use in screening xenograft recipients for each of the known common infectious agents derived from swine. Very sensitive epidemiologic techniques (routine specimen collection and archiving from subjects and close contacts) and diagnostic methods (novel and mechanistically redundant testing strategies) have been developed that will permit productive investigation of a suspicious syndrome in a xenograft recipient, should one occur.

An array of sensitive, "unbiased" DNA-, RNA-, and protein-based diagnostic techniques exist that are likely to greatly facilitate detection, identification, and containment of currently unknown xenograft-associated infectious agents, if any exist.

IV. Need for evidence to reduce the current risk-benefit ratio

There was a general agreement during the discussion that new evidence would be necessary to reduce the current risk-benefit ratio, and justify altered (potentially less stringent) criteria for patient enrolment into clinical trials. To reduce the risk-benefit ratio associated with any proposed clinical xenograft trial, either **confirmation of absence of actual infection in prior xenograft recipients** or reproducible evidence of **improved efficacy** in an informative preclinical model would be required.

The group agreed that the experience of patients with relevant prior exposures in xenotransplantation trial would provide the best available evidence regarding xeno-associated infection risks. Any available prior xenograft recipients' samples should be tested for xenozoonosis markers in order to better quantify risks of infection occurrence and transmission. Whenever possible, recipients' fresh and / or aliquotted biorepository samples should be investigated with contemporary techniques able in particular to detect slow or occult infections. There was a concern that archived samples may not provide reliable results due to lack of correct storage. The quality of storage must be documented if archived samples are used.

It must be clear that negative results from testing of samples associated with prior xenograft experiences will not retrospectively "legitimize" old studies if they were originally performed under ethically suspect circumstances, and would not be sufficient justifications for resuming non-therapeutic trials.

Many patients exposed to xenogeneic cell or organ transplants can be identified (e.g. in Belarus, China, Czech Republic, Germany, Mexico, New Zealand, Russia, Sweden, Ukraine, USA…etc). No symptomatic problems have been reported in association with these experiences, although systematic surveillance is generally lacking.

Investigations to document possible transmitted xenozoonosis in patients exposed to animal transplants is part of the project XENOME funded by the European Commission. It focused on

patients treated at the Prague burn centre with full thickness porcine skin from commercial animals from the food chain.

V. Testing for xenozoonosis

Laboratories leading in the development and practice of testing methods for xenozoonosis, PERV in particular, are exchanging samples and rely on each other's published methods to progress (Linda Scobie, Yasu Takeuchi and Joachim Denner, Jay Fishman and Ralf Tonjes inter alia).

Participants discussed the importance of optimizing the reliability (sensitivity, specificity, ease of accurate general use) of tests for xenozoonosis. Considering the features of current "best available" technology, participants agreed that a core group of specialized infectious disease reference laboratories (certain public health authorities and academic laboratories) with recognized expertise in xenozoonosis should serve as a global reference. These laboratories could provide global guidance and advice and possibly develop external quality assessment schemes (EQAS) for the most important xenozoonosis agents. This core group of existing specialized infectious disease reference laboratories, as well as other public health or academic laboratories with potentially relevant expertise or unique resources, should ideally be convened to support improved assay development, validation, standardization, and sample throughput. Such collaborative work between reference laboratories should be supported by national health authorities and institutions and trial sponsors, and facilitated by WHO. A first step would be the convening of a first consultation to assess the situation and define priorities and plan of work .

VI. Biorepository

The need for reliable sample acquisition and archive permanence mandates robust sample collection and identification protocols under a quality management system. The participants consider that sample redundancy is a necessity, and recognize that outsourcing to existing biobanks will often be considered a necessary investment.

The value for future investigations of documentation and in particular of archived samples led the Changsha Principles, which include a recommendation that the clinical trial authorization file contains a provision for the preservation of all records, data and archived samples in case the trial proposers become unable to continue the trial.

One solution could be the transfer of trial records, data, and archived samples to the relevant regulatory authority (ies) or another designated organization. To avoid this becoming a burden for competent authorities specific insurances should be detailed in the trial authorization file.

VII. Existing WHO alert and response mechanisms

In the area of emerging infectious threats, WHO has established world health surveillance and reaction mechanisms through the coordination of Member States' responsibilities. These mechanisms have recently been tested by SARS, H1N1, and a variety of food-borne outbreaks. These epidemics have demonstrated that an effective global alert and response system is in place.

The WHO Global Outbreak Alert and Response Network, GOARN, is a technical collaboration of existing institutions and networks that pools human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance (Thomas Grein). The Network provides an operational framework to link this expertise and skill to keep the international community constantly alert to the threat of outbreaks and ready to respond. The global alert and response system appears to be adequate – from health authority infrastructure perspective – to detect, measure, manage, report, and respond to any anticipated or unanticipated xeno-associated infection.

The International Health Regulations (IHR) are not limited to specific or even known diseases. While IHR are not a substitute for specific regulation of xenograft-specific risks, they are broad enough to cover at least some of the risks in the context of xenotransplantation (Bruce Plotkin). IHR requirements provide a regulatory framework to support international response to an unanticipated xenozoonosis: they define each Member State's health authority's responsibility to survey, report, inform, and control risk of interpersonal or cross border transmission of a xeno-associated infection. The effectiveness of these mechanisms in response to the HlNl and SARS epidemics justify cautious confidence that xenotransplantation trials that are designed and conducted in accordance with Changsha Communiqué recommendations are likely to mitigate xeno-associated health risks and protect public health.

In case of xenotransplantation associated events it is necessary

- to identify any xenozoonosis transmission to a recipient by early investigation and
- to presume a risk of human to human transmission in the case of a new xenozoonosis

The private entity conducting the trials has the responsibility to inform the competent governmental authority. The competent authority will contact the national governmental unit responsible for assessing events and coordinating event reporting to the World Health Organization under the International Health Organizations (2005), if any of the following are suspected:

(a) human-to-human transmission or a significant risk of that transmission,

(b) A product or animal used or to be used in xenotransplantation is discovered to be infected or contaminated so as to be potentially harmful to humans and is imported or exported internationally.

VIII. Review of Changsha Principles and Guidance

Participants unanimously concluded that current scientific, regulatory, and legal tools, applied in the context of rigorous adherence to the Changsha Communiqué's principles and recommendations, appear to be adequate to protect public safety.

Based on a detailed review of current xenotransplantation activity, interim progress with respect to basic science, current prospects for therapeutic clinical application, and infectious

disease considerations, the attendees agreed that the principles and guidance contained in the Changsha Communiqué remain valid and fully actionable.

IX. Need for Transparency and International Collaboration

During the discussions it appeared that better information on xenotransplantation trials and activities taking place in Member States is necessary to harmonize practices and facilitate collaborations. The participants were asked to consider whether, in addition to established guidelines, a "Principle of Transparency" should be applied to the design and conduct of planned xenotransplantation clinical trials.

Acknowledging patient privacy rights and commercial confidential information, the participants unanimously encourage and strongly support:

1) Transparency in the conduct of any xenotransplantation trial, including (but not limited to) the design of the trials and the development of national policies and procedures to regulate them.

2) Timely independent data review as an important tool to help detect, understand, and mitigate risks, in particular infectious, that may be associated with conduct of xenotransplantation trials.

3) Timely notification of likely or known health risks, as well as periodic notification of absence of detected infection, should occur in accordance with Health Authorities' requirements and WHO's recommendations

4) The response to a perceived infectious risk should include a prompt,' comprehensive consultation process with global experts, health authorities and relevant competent authorities to evaluate and respond to the threat, in accordance with established WHO policies.

In general transparency in the conduct of any xenotransplantation trial, including sharing the design of xenotransplantation trials and their development as well as the elaboration process for national policies and procedures, should be seen as a good practice enabling the benefit of experience and expertise. Timely independent reviews are important tools to help detect, understand, and mitigate infectious risks that may be associated with xenotransplantation trials.

X. Conclusion and Recommendations

In general the specificity of each xenotransplantation project makes it difficult to provide generic guidance beyond the Changsha Communiqué.

Participants recognized that this specificity as well as the need to react in a timely and appropriate manner to any suspicion of xenozoonosis transmission, lead to encourage global exchanges of information. Therefore mechanisms are necessary to access advice from the most

experimented experts both for the prevention and, should the case arise, the investigation of incident.

A. Recommendation to WHO

1) To facilitate global collaboration for laboratory investigations

WHO should facilitate the creation of a collaborative group of public/ academic xeno-related infectious disease reference laboratories and appropriate Health Authorities' resources to support assay development, validation, standardization, and sample throughput. Such a network would include representation of CDC, FDA, Paul Ehrlich, NHMRC of Australia or NZ, Korea CDC, Chinese CDC…etc. Once this resource is established, any proposed xenotransplantation trial should consider access to this resource, as part of the protocol and /or case of incident. In exchange for cost-efficient access to this resource, the community expects that resulting data will be published after consideration of commercial proprietary concerns.

2) To encourage transparency in xenotransplantation related activities

Transparency in the development of national policies and procedures and in the conduct of any xenotransplantation trial, including (but not limited to) the design of xenotransplantation trials is essential to ensure harmonized practices and level of safety. Timely independent review is a valuable additional tool to help prevent, detect, understand, and mitigate infectious risks that may be associated with conduct of xenotransplantation trials.

3) To convene regular global consultations on xenotransplantation activities

WHO should foster regular (annual or biennial) interaction between regulators and xenotransplantation subject matter experts, as appropriate to the level of contemporary xenotransplantation activity. This global consultation would discuss planned or on-going xenotransplantation clinical activities, provide a framework for exchanges identifying needs for advice and collaborations

B. Recommendation to Member States, Investigators, Proposers, or Study Sponsors

1) To seek global consistency in requirements for clinical trials by referring to best global standards and experts' advice.

   Member States Health Authorities (MSHA), investigators, proposers and study sponsors should follow the requirements expressed by the Changsha Communiqué, refer to consensus standards and/or to regulatory guidance whenever applicable and consult experts from the scientific community and other MSHA, including for external audits, regarding:

   - Source donor animal. The list of potentially infectious organisms that should be excluded from source animals for a xenotransplant trial defined according to best current evidence

- Recipients, family members and close contacts surveillance, tailored to results of testing in the source animal and including regular sample collection and redundant specimen archiving defined, required, and enforced according to best current evidence.
- Routine surveillance testing and for-cause analytic strategies should be defined, required, and enforced based on sample collection approaches used for Recipient Surveillance, and should assure access to state-of-the-art diagnostic methodology.
- Risk/Benefit analysis. A favourable risk/benefit profile is essential to the ethical conduct of a clinical xenotransplantation trial. (Good Process is exemplified by IXA consensus documents for islet transplantation.)
- Trial infrastructure. Practical implementation and safe execution of a xenotransplantation trial require sophisticated regulatory oversight, testing capability, and research infrastructure. In addition to putting in place regulations to govern xenotransplantation that are consistent with the principles and recommendations of the Changsha Communiqué, Member States that wish to permit a xenotransplantation trial but that lack this scientific expertise or infrastructure should access available international expertise before approving such a trial.

2) To combat unfounded assertions on human xenotransplantation

Stakeholders in xenotransplantation should only communicate on the basis of evidence. In particular Member States should implement regulations that prohibit statements or advertisements for xenotransplantation trials or products that claim unproven benefits, or that are (or may prove to be) false or misleading with respect to known or unknown risks.

3) To refer to experienced independent laboratories

- Member States, Investigators, Proposers, and/or Sponsors of a clinical trial should assure access to identified expertise in xeno-specific disease assays. Laboratory qualifications should be appropriate to accomplish high quality, reliable, standardized sample processing, storage, and testing, as appropriate to accomplish specific investigative or research goals, respectively.
- Member States should consider assuring access to an independent (third party) reference laboratory with identified expertise in xeno-specific infectious disease assays.

Annex 1

Resolution WHA57.18

Human organ and tissue transplantation

The Fifty-seventh World Health Assembly,

Recalling resolutions WHA40.13, WHA42.5 and WHA44.25 on organ procurement and transplantation;

Having considered the report on human organ and tissue transplantation[1];

Noting the global increase in allogeneic transplantation of cells, tissues and organs;

Concerned by the growing insufficiency of available human material for transplantation to meet patient needs;

Aware of ethical and safety risks arising in the transplantation of allogeneic cells, tissues and organs, and the need for special attention to the risks of organ trafficking;

Recognizing that living xenogeneic cells, tissues or organs, and human bodily fluids, cells, tissues or organs that have had *ex vivo* contact with these living xenogeneic materials, have the potential to be used in human beings when suitable human material is not available;

Mindful of the risk associated with xenogeneic transplantation of the transmission of known or as yet unrecognized xenogeneic infectious agents from animals to human beings and from recipients of xenogeneic transplants to their contacts and the public at large;

Recognizing that transplantation encompasses not only medical but also legal and ethical aspects, and involves economic and psychological issues,

I Allogeneic transplantation

1. URGES Member States:

(1) to implement effective national oversight of procurement, processing and transplantation of human cells, tissues and organs, including ensuring accountability for human material for transplantation and its traceability;

(2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices in the procurement, processing and transplantation of human cells, tissues and organs, including development of minimum criteria for suitability of donors of tissues and cells;

(3) to consider setting up ethics commissions to ensure the ethics of cell, tissue and organ transplantation;

(4) to extend the use of living kidney donations when possible, in addition to donations from deceased donors;

(5) to take measures to protect the poorest and vulnerable groups from "transplant tourism" and the sale of tissues and organs, including attention to the wider problem of international trafficking in human tissues and organs;

2. REQUESTS the Director-General:

[1] Document A57/17.

(1) to continue examining and collecting global data on the practices, safety, quality, efficacy and epidemiology of allogeneic transplantation and on ethical issues, including living donation, in order to update the Guiding Principles on Human Organ Transplantation2;
(2) to promote international cooperation so as to increase the access of citizens to these therapeutic procedures;
(3) to provide, in response to requests from Member States, technical support for developing suitable transplantation of cells, tissues or organs, in particular by facilitating international cooperation;
(4) to provide support for Member States in their endeavours to prevent organ trafficking, including drawing up guidelines to protect the poorest and most vulnerable groups from being victims of organ trafficking;

II Xenogeneic transplantation

1. URGES Member States:
(1) to allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place;
(2) to cooperate in the formulation of recommendations and guidelines to harmonize global practices, including protective measures in accordance with internationally accepted scientific standards to prevent the risk of potential secondary transmission of any xenogeneic infectious agent that could have infected recipients of xenogeneic transplants or contacts of recipients, especially across national borders;
(3) to support international collaboration and coordination for the prevention and surveillance of infections resulting from xenogeneic transplantation;

2. REQUESTS the Director-General:
(1) to facilitate communication and international collaboration among health authorities in Member States on issues relating to xenogeneic transplantation;
(2) to collect data globally for the evaluation of practices in xenogeneic transplantation;
(3) to inform proactively Member States of infectious events of xenogeneic origin arising from xenogeneic transplantation;
(4) to provide, in response to requests from Member States, technical support in strengthening capacity and expertise in the field of xenogeneic transplantation, including policymaking and oversight by national regulatory authorities;
(5) to report at an appropriate time to the Health Assembly, through the Executive Board, on implementation of this resolution.

(Eighth plenary meeting, 22 May 2004 – Committee A, third report)

[2] Document WHA44/1991/REC/1, Annex 6.

Annex 2

First WHO Global Consultation on
Regulatory Requirements for Xenotransplantation Clinical Trials
Changsha, China, 19-21 November 2008

The Changsha Communiqué[3]

Principles

1. Successful xenotransplantation has the potential to treat a wide range of serious diseases such as diabetes, heart and kidney disease. Successful xenotransplantation could provide transplants for people who currently would not get a transplant.

2. Potentially animals could provide a plentiful supply of readily available, high quality cells, tissues and organs for transplantation. Genetic modification of the animals may improve the effectiveness of such xenotransplant material. Animals used in xenotransplantation should be from a closed herd bred for the purpose and housed in a well-controlled, pathogen-free environment with high standards of animal welfare. Source animals should be extensively tested to ensure freedom from known pathogens with appropriate biosecurity and surveillance in place to ensure continued freedom from infectious disease.

3. Xenotransplantation is a complex process which carries risks, including graft rejection, inadequate graft function and transmission of recognized or unrecognized infectious diseases to the recipient. There is the risk of developing serious or novel infections which could infect not just the transplant recipient but also close contacts or the wider human or animal populations.

4. Because of these wider community risks, xenotransplantation clinical trials and procedures need to be effectively regulated. There should be no xenotransplantation in the absence of effective regulation by the government of the country. Regulation should have a legal basis with powers to ban unregulated procedures and enforce compliance with regulatory requirements. The regulatory system should be transparent, must include scientific and ethical assessment and should involve the public.

5. Because of the community risk, in proposed clinical trials of xenotransplantation there should be a high expectation of benefit to balance the risk. The level of this expectation should be in proportion to the level of the risk. The level of safety and efficacy should conform to recommendations from the international scientific community, when available, and requires rigorous pre-clinical studies using the most relevant animal models. Proposers of trials must provide all the information required by the regulatory authority to assess the risks and determine how the risks can be minimised.

6. Proposers of xenotransplantation clinical trials must be able to clearly justify carrying out a particular trial on a specific patient population. Patient selection should be on the basis of informed consent from motivated patients willing to accept the special conditions that will be required by the trial. Patients and close contacts should be effectively educated about their treatment to encourage compliance, and to minimize risks for themselves and for society.

[3] Disclaimer: These are the conclusions of the above meeting for which WHO was the Secretariat.
These conclusions do not necessarily represent the decisions and policies of WHO.

7. Participation in xenotransplantation will usually require the long term storage of animal and patient samples, pre- and post-treatment, as well as records. It will require life-long follow up of recipients and possibly their close contacts. There must be rigorous analysis of trial outcomes. Xenotransplant product recipients must be registered in an appropriate database with traceability to the donor animal, while ensuring that patient privacy is protected. If anything happens to prevent the proposers from continuing the trial, there must be an adequate provision for all records, data and archived samples such as their transfer to the regulatory authority or other designated organization.

8. Medical teams must have appropriate expertise and understand the risks to the patients, themselves and the community. Because of the risk of infectious disease for the community, there must be a system in place for vigilance and surveillance with contingency plans to identify and respond to any indication of xenotransplantation related infection in a timely manner.

9. There needs to be a global system for exchanging information, preventing unregulated xenotransplantation, providing support for states and coordinating xenotransplantation vigilance, surveillance and response to suspected infections.

10. Because of the potential benefits of successful xenotransplantation, consideration should be given from the beginning to future equitable access to this therapy and the public sector should be encouraged to support xenotransplantation research and development.

Key Recommendations

To WHO

1. WHO should have a dedicated resource to develop and support a plan for global action for xenotransplantation.

2. WHO should inform Member States of the need to assess xenotransplantation practices in their territories.

3. WHO should encourage and, if requested, support Member States to the extent possible in assessing their capacity to regulate xenotransplantation and in identifying xenotransplantation practices in their territories.

4. WHO should promote public awareness of the potential benefits of successful xenotransplantation and of the dangers of unregulated xenotransplantation, including xenotourism.

5. WHO should have in place a system for the identification of and response to any xenotransplantation infectious disease outbreak in a timely manner.

6. WHO should continue its support to the database of worldwide xenotransplantation practices.

7. WHO should maintain a register of xenotransplantation trials and a list of experts who can advise Member States on aspects of xenotransplantation and of specialized laboratories able to test for xenotransplantation-related pathogens.

8. WHO should promote future equitable access to successful xenotransplantation products.

To Member States

1. Member States should take immediate steps to identify any xenotransplantation practices in their territories and ban those that are unregulated. They should promote public awareness of these practices and their risks.

2. Member States should ensure that public health officials are aware of the infection risks of xenotransplantation, including those associated with patients travelling to receive xenotransplantation products outside their territories and have plans in place to timely identify and respond to any such infection.

3. Member States should review their laws to determine whether they have adequate authority to regulate xenotransplantation, ban unregulated xenotransplantation and provide appropriate sanction for failure to comply.

4. Member States should assess whether they have the resources and capacity to regulate xenotransplantation effectively. If they do not have such resources and capacity, they should ban xenotransplantation in their territories.

5. If a Member State has the capacity to regulate xenotransplantation and believes xenotransplantation should be carried out, it should ensure there is an effective national registry and regulatory process in place.

To investigators and proposers of clinical trials using xenotransplantation products

1. Investigators must ensure that source animals are bred for the purpose and as safe as possible, using a closed colony of consistently known specific pathogen-free animals housed in a well controlled pathogen-free environment with high levels of biosecurity.

2. Investigators must provide clear justification for the trial, including adequate preclinical data on safety and efficacy, usually from non-human primate testing.

3. Investigators should select trial participants for whom there is no adequately effective alternative therapy available and who understand the risks and consequences of the procedure, including the need for compliance with life-long follow up and who are motivated to modify their behavior.

Annex 3

Available guidance documents on xenotransplantation

Guidance and consensus documents describe current consensus perspectives of regulatory requirements for xenotransplantation clinical trials in more detail, for instance

per type of xenograft

The International Xenotransplantation Association Consensus Statement on Conditions for Undertaking Clinical Trials of Porcine Islet in Type 1 Diabetes
http://www.med.nagoya-u.ac.jp/tx-immunology/xeno/ECE3E929-31FC-41FB-A7DB-E6B311A05C65_files/Consensus%20Clinical%20Xeno%20Islet%20Tx%20.pdf

per process requirements

FDA Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm074354.htm

or for infectious risk management

World Health Organization (1998): Xenotransplantation: Guidance on Infectious Disease Prevention and Management
WHO/EMC/Z00/98.1
http://www.who.int/transplantation/publications/WHO_EMC_ZOO_98.1.pdf

OECD/WHO Consultation on Xenotransplantation Surveillance: Summary
WHO/CDS/CSR/EPH/2001.1
http://www.who.int/transplantation/publications/OECD_WHO.pdf

WHO Guidance on Xenogeneic Infection/Disease Surveillance and Response: A Strategy for International Cooperation and Coordination
WHO/CDS/CSR/EPH2001.2
http://www.who.int/transplantation/publications/OECD_WHO2.pdf

Annex 4

Xenotransplantation-associated Infectious Risk: A Background Paper for the Second WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

Jay A. Fishman*#, Linda Scobie+, and Yasuhiro Takeuchi^

* Transplantation Infectious Disease and Compromised Host Program, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA.

+ School of Health and Life Sciences, Glasgow Caledonian University, Glasgow, UK

^ Wohl Virion Centre, Division of Infection and Immunity, University College London, London, UK

Corresponding author: jfishman@partners.org

Acknowledgements: This document was prepared to support discussions at the World Health Organization Second Global Consultation of Regulatory Requirements for Xenotransplantation Clinical Trials, Geneva, October 17-19, 2010. The authors are grateful for the expert editorial assistance of Luc Noel, Ralf Toenjes, Joachim Denner, Yannick Blanchard, Emanuele Cozzi, and Takaaki Kobayashi. JAF's research has been supported by NIAID 2010A056237 and P01AI45897. LS's and YT's research has been funded by the European Sixth Framework Programme (Life Science, Genomics and Biotechnology for Health) funded project XENOME, LSHB-CT-2006-037377.

Outline

Overview:

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. This definition may include human bodily fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues, fluids or organs. The definition may also include non-living or acellular biomaterials (e.g., heart valves, blood vessels, tendons) derived from non-human species. These latter non-viable tissues have a much reduced potential for the spread of infection but may elicit immune or other host responses. As with any form of transplantation, xenotransplantation carries the potential risk of the transmission of infection with the cells or tissues of the graft1-8. In xenotransplantation, there is the unique potential risk for the transmission of both known and unknown zoonotic infectious agents of animal origin into human recipients and into the wider human population. Thus, the term "xenosis" (also "direct zoonosis" or "xenozoonosis") was coined to reflect both the unique epidemiology of infection of source animals used for xenotransplantation and experience with immunocompromised patients that indicates that novel pathogens may emerge as a cause of infection, including organisms not normally associated with human disease2,6. The degree of risk is unknown in the absence of clinical trials. The clinical application of xenotransplantation has important implications for infectious disease surveillance, both at the national and international levels. As a result, World Health Organization Resolution WHA57.18 emphasizes that members states should "allow xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms overseen by national health authorities are in place9. This issue was further defined in the Changsha Communiqué of the First WHO Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials (Changsha, China, 19–21 November 2008)10. The Changsha Communiqué stated that, in light of potential risks to xenograft recipients and to the broader community that "there should be no xenotransplantation in the absence of effective regulation by the government of the country. A series of useful guidance for xenotransplantation have been issued by the U.S. Food and Drug Administration and other national authorities11-15. WHO has also previously provided a series of guidance documents related to xenotransplantation16,17.

Preclinical data indicate that infectious disease events associated with clinical xenotransplantation from swine, should they occur, will be rare; data in human trials are limited but have demonstrated no transmission of porcine microorganisms including porcine endogenous retrovirus (PERV)18-21. This document will summarize approaches to disease surveillance in individual recipients of nonhuman tissues. Some general concepts may be useful:

• The risk for infection is related to the properties of the specific organism, the quantity of the organism transmitted, the availability of appropriate machinery (e.g., receptors, nutrients) in the host, and the immune competence of the host. It is not possible to predict the precise behavior of unidentified, animal-derived pathogens in human hosts or the range of clinical manifestations that may occur.

• Investigation of suspected xenogeneic infection events (xenosis, xenozoonosis) should be performed in collaboration with an expert data safety review panel and the appropriate public health and competent authorities. Expertise in the diagnosis and management of infections in immunocompromised hosts should be available for trials using immunosuppression. Reporting of such

events should be expedited to allow optimal care of the recipients and investigation of their contacts so as to reduce the possibility of dissemination of infection.

• It should be considered an obligation of performance of xenotransplantation trials to report outcomes, including any infectious disease transmissions, in the scientific literature while protecting the confidentiality of individual patients and investigators

• Xenotransplantation will necessitate the development of surveillance programs to detect known infectious agents as well as previously unknown or unexpected pathogens in the absence of recognizable clinical syndromes. This may include assays for known infectious agents, probes for classes of infectious agents (e.g., common genes or antigens of herpesviruses), and assays for unknown pathogens in a variety of tissues.

• Microbiological assays will require standardization of procedures and validation by expert and/or reference laboratories. Such validation may necessitate the use of regional or reference laboratories and shared reagents, laboratory practices and methods. Such reference laboratories may require international collaboration.

• Repositories of samples from source animals and from recipients prior to, and following xenograft transplantation are essential to the investigation of possible infectious disease events. As a result, such repositories will need to be maintained for prolonged periods of time (i.e., many years).

• An ideal data repository for xenotransplantation data requires standardized definitions of terms and allows the international sharing of de-identified microbiological data via secure web-based applications.

• The public should be engaged in discussions regarding infectious risks given recent public reactions to some innovations in biotechnology (e.g., in the application of genetic technologies to the agriculture and food industries).

In general, it is likely that the development of surveillance techniques might be guided by the "Precautionary Principle." That is, the risk of xenogeneic infection is generally thought to be low but the deployment of appropriate procedures and assays should not wait until a risk is confirmed22. This concept includes implementation of appropriate assays and emergency protocols in advance of clinical trials as well as further improvement of surveillance technologies to facilitate future trials. All assays require training, standardization and validation, and, given the relatively small number of clinical samples, sharing of laboratory methods and expertise will be needed to optimize the quality of the surveillance and diagnostic services provided.

Concerns over the potential hazards associated with xenotransplant procedures tend to overshadow the potential benefits. Careful microbiological screening of source animals used as xenotransplant donors may enhance the safety of transplantation beyond that of allotransplant procedures. Xenogeneic tissues may be relatively resistant to infection by human pathogens such as HIV, HTLV and the hepatitis viruses which could be beneficial to individuals undergoing xenotransplantation4. Moreover, xenotransplantation may be made available at the time when patients require organ replacement on a

clinical basis, possibly on a more timely basis than organs from deceased human donors. The insights gained in basic studies of microbiology and immunology in xenotransplantation will benefit many individuals in years to come.

Targets of Surveillance Activities

1. Recipients of xenotransplantation products.

2. Sexual or close contacts of xenograft recipients.

3. Source animals, animal handlers, and facilities

4. Medical care providers

Donor-derived infections have been detected in multiple clusters of allotransplant recipients receiving grafts from a single, infected donor23-26. Experience in this area has allowed the evaluation of such recipients to be divided into three general categories: common infections known to be transmitted frequently with viable cells or organs (e.g., cytomegalovirus [CMV]), uncommon infections (e.g., lymphocytic choriomeningitis virus [LCMV]), or unknown pathogens, presenting as an infectious syndrome (e.g., fever) or as asymptomatic infection (e.g., resulting in positive serology). A similar approach will be needed for the evaluation of xenograft recipients. Investigations will be based in a number of categories that reflect differing urgency and implications for clinical trials of xenotransplantation:

1. Routine surveillance of healthy source animals (screening)

2. Routine surveillance of recipients (screening) pre- and post-transplantation (e.g., microbiologic testing for specific agents (e.g., porcine endogenous retrovirus [PERV] by serology and/or nucleic acid testing [NAT] as dictated by the monitoring protocol such as every three months for five years) following the transplant, then at appropriate intervals for the life of the xenograft recipient.) Microbial assays that are performed in the absence of clinical symptoms or other abnormalities may provide epidemiologic data useful in the assessment of safety in clinical trials.

3. Routine evaluation of social and sexual contacts of xenograft recipients, possibly including household pets.

4. Evaluation of infectious syndromes (e.g., fever of unknown origin [FUO], leukocytosis, leukopenia, graft dysfunction, pneumonia, hepatitis, abscess formation) in xenograft recipients, including:

- Exclusion of syndromes commonly associated with allotransplantation (e.g., CMV) or due to immunosuppressive drugs or to technical/surgical adverse events.

- Evaluation of PERV infection by serologic and NAT testing.

- Assessment of other recipients of xenografts derived from the same herd or source of swine.

• Evaluation of sexual and close social contacts of recipient (and medical care providers as appropriate) after identification of infectious syndrome in the recipient

• Investigation of recipients for unknown pathogens or organisms not previously associated with clinical syndromes in humans.

Any indication that the infectious syndrome is related to the xenotransplantation procedure would place a temporary hold on further trials using the source animal herd until the identification and source of the presumed infection is determined. Consideration may be given to hospital admission and isolation of the individual based on the clinical protocol, the level of perceived risk to the community and local regulations.

Investigations would require testing of the source animal (archived specimens and/or herd) and recipient including, but not limited to (see details below):

• Cultures and examination of blood, urine, sputum, stool, cerebrospinal fluids (as appropriate) for bacteria, fungi, viruses, parasites

• Testing for common human pathogens of immunocompromised hosts depending on the clinical syndrome (CMV, Epstein Barr virus [EBV], Cryptococcus neoformans, mycobacteria, Nocardia species, Pneumocystis jirovecii)

• Specific porcine pathogen testing (PERV, porcine cytomegalovirus [PCMV], porcine lymphotropic herpesvirus [PLHV], circovirus, hepatitis E virus and others – see Tables 1 and 2)

• High throughput sequencing of nucleic acids derived from sera or cell samples using non-biased random or degenerate primers (search for unknown pathogens)26

• Co cultures on permissive cell lines.

The clinical trial would resume with approval from the institution and public health authorities if the causal agent (or other etiology) is identified and found to be treatable and there is no evidence of transmission to contacts of the xenograft recipient. Decisions regarding the subsequent use of the herd of source animals would be based on whether the infectious agent is present in the herd and whether it can be excluded from the herd. In the absence of a specific diagnosis, resumption of the trial would be assessed based on review of clinical data by experts external to the trial and by the appropriate competent authority.

“Certainty of Diagnosis” in Surveillance

Early investigation, diagnosis/detection and reporting are essential features of any surveillance system developed for xenotransplantation and for the optimal care of xenograft recipients. Confirmation of a microbiological diagnosis may require levels of sophistication in clinical laboratories not available to all clinical centers. Laboratories should perform validated assays in facilities accredited according to national standards. International reference laboratories may serve as highly specialized resources for

national research programs. Such inter-laboratory collaboration may provide an additional degree of certainty regarding microbiological assays. Any “in-house” (non-commercial) assays require validation. The use of highly sensitive assays risks generation of false positive results and misinformation for patient and public health authorities. Confirmation of laboratory data should be consistent with optimal clinical care while protecting public interests. The infectious and pathogenic potential in humans of various organisms derived from swine is generally unknown unless the same or similar organisms infect humans – in which instance derivation from source animals may be suspect. A confounding variable may be whether the recipient has been in contact with or, in some cases, consuming, animal-derived proteins or cells (e.g., porcine insulin, pancreatic lipases, heparin) which might affect certain assays (e.g., antibody assays). These may be potential sources of infection by specific viruses surviving manufacturing processes. The role of such products as a potential source of infection or false positive assays merits clarification.

The presence of an organism in the xenograft itself, while undesirable, is not a clear predictor of the risk of infection for that individual or their contacts. Thus, if the organism cannot replicate in human cells or disseminate within the human host, the risk of infection is likely to be limited.

The need for accurate microbial diagnosis is emphasized by the need to share validated information with other patients who have received similar xenotransplantation products or grafts from animals of the same source herd, and to test such individuals for infection.

Levels of responsibility

The performance of clinical trials in xenotransplantation and the initial responsibility for the recognition and investigation of possible infectious complications rests with the medical center performing clinical trials, the primary physicians providing clinical care, and local clinical laboratories. These individuals must be aware of the public health implications of possible infectious disease transmissions with xenografts, and have a strategy in place for the initial collection, processing and storage of clinical samples, the potential need for isolation of the xenograft recipient, and the notification of public health and competent authorities.

Public health authorities must retain oversight for the maintenance of routine records and archiving of specimens, the implementation of proper investigations of xenogeneic infection events, and the communication of data to the appropriate competent authorities. The requirements placed on source herd development and laboratory testing will vary with local regulations. It is reasonable to consider "good manufacturing practices" (GMP) and good laboratory practice (GLP) in which the quality of manufacturing processes and laboratory techniques are clearly defined and controlled and critical processes carefully validated.

Specific Pathogens – General Considerations

Potential human pathogens derived from animals can be categorized according to the likely behavior of related organisms in allotransplant recipients (Table 1).2,4,8 Xenotransplantation may enhance the risk of graft-derived infection because recipients generally lack preformed immunity, clinical laboratory assays may not be available, incompatible major histocompatibility antigens may reduce the efficacy of host cellular immune responses, and because of unknown effects of genetic or other manipulations of source animals used to improve xenograft immune compatibility or to reduce physiologic (e.g., of the coagulation system) incompatibilities. For instance, human complement regulatory proteins introduced into swine to overcome hyperacute rejection (HAR) may serve as receptors for human viruses.

The recognition of infection in immunocompromised hosts is more difficult than in normal individuals because signs of infection such as inflammation may be absent. In this setting, animal-derived infections may go undetected against the high background incidence of infection in immunosuppressed transplant recipients. Difficulty in predicting which animal-derived organisms are likely to act as pathogens in human recipients is compounded when such organisms do not cause disease in native host species or acquire new characteristics (e.g., via genetic recombination or mutation) in a human host. The virulence of some organisms may increase with passage in a new host through adaptation.

Common Pathogens in the Immunocompromised Host

Based on experience with immunocompromised human transplant recipients and with immunosuppressed swine and primate recipients of porcine xenografts, lists of microorganisms of swine that could be associated with human infection can be made (Table 2). Ideally, such organisms could be eliminated prospectively from source animals that could be considered “designated pathogen-free” (DPF) for xenotransplantation purposes. Additionally, animals may be bred to exclude some porcine herpesviruses (PCMV) or porcine circoviruses (PCV1, PCV2). If not excluded from the donor herd, this list also provides some basis for investigation of infectious syndromes in xenograft recipients. It should be noted that most serological assays for viruses may not be species-specific and will not distinguish between porcine and human pathogens, e.g., circovirus, hepatitis E virus, porcine parvovirus (PPV). Depending on the strategy developed for the screening, routine evaluation, and diagnostic testing of source animals and recipients, local regulatory bodies and competent authorities should require that these assays be validated in accredited clinical laboratories prior to the commencement of any xenotransplantation trials.

The list of microorganisms may vary with the use intended for various specific xenografts. Thus, encapsulated cells placed in the brain may pose a different risk from that posed by either a heart or liver xenograft. Although such lists provide a basis for screening source animals and recipients, these microbiological standards need to be dynamic and subject to frequent review and updating. To exclude infectious agents and to prevent their reintroduction or spread into animal herds, special facilities for housing source animals (e.g., barrier facilities) are needed. However, the precise manner for meeting these goals need not be uniform so long as microbiologic hazards are excluded or appropriately minimized.

Retroviruses:

Concern about retroviral transmission in xenotransplantation relates to the potential for "silent" transmission, i.e., unapparent infection that may cause altered gene regulation, oncogenesis, or recombination1,3,4,7,27. No exogenous viruses, equivalent to HTLV or HIV, have been found in pigs. However, endogenous retroviruses (part of the germ line DNA) have been demonstrated in all mammalian species studied to date. Endogenous retroviruses that are infectious for human cells in vitro have been detected in many species including baboons (BaEV), cats (RD114), mice (murine ERV), and pigs (PERV). Although the pig genome contains sequences closely related to mouse mammary tumor virus or Mason-Pfizer monkey virus (betaretrovirus) and murine leukemia virus (gammaretrovirus) sequences, only three subgroups of gammaretrovirus PERV (PERV-A, -B, -C) have been identified in swine that possess infectious potential28-30,32-36. Two of these, PERV-A and -B, can infect pig cells and several human cell lines and primary cell cultures in vitro30,35,37,38. The third sub-group, PERV-C, infects porcine cells only30. Infectious forms of the remaining PERV families have not been isolated and are unlikely to encode infectious virus due to disruptions in open reading frames (ORFs)32. PERV mRNAs are expressed in all pig tissues and in all breeds of swine tested to date; expression can be amplified by stimulation of swine peripheral blood lymphocytes in vitro.31,34,35,38 There is variation between tissues in terms of the size and amount of PERV mRNA transcripts, consistent with in vivo recombination and/or processing27,34. High-titer human-tropic PERV (HTHT-PERV) are recombinants between PERV-A and PERV-C sequences. Although the site of recombination varies, viral sequences are derived from the recombination of PERV-A elements with the post-VRA (envelope) region of PERV-C31,35,38,39. Therefore, although PERV-C is not capable of infecting human cells, it appears to be an essential component of HTHT-PERV and important in the assessment of infectious risk associated with PERV in xenotransplantation35,38,40. The source of these recombinants in vivo is unknown. However, recombinant PERV-AC sequences have been found in the cellular DNA of some miniature swine capable of infection of human cell lines in vitro27. It is not known whether these elements result from autoinfection following exogenous viral recombination or are pre-existing proviral elements. No evidence of PERV infection has been demonstrated of human cells in vivo and no disease due to this family of viruses has been described in swine or humans to date. PERV appears to be susceptible to certain currently available antiviral agents41,42.

Assays Related to Porcine Endogenous Retrovirus (PERV)

Assays for PERV may be used prior to xenotransplantation in the selection of the "safest" animal donor and after the procedure to detect evidence of PERV transmission in the recipient. Although it is extremely difficult, if not impossible, to eliminate all PERV from the genomes of pigs, it is possible to select source animals with phenotypes consistent with reduced capacity for PERV transmission to human cells. Current terminology includes a "non-transmitter" animal which transmits PERV to pig, but not human cells; a "null" animal does not transmit PERV to either human or pig cells in vitro31,35,43. It has been observed that the non-transmitter or "null" phenotype is not stable and that transmission can be demonstrated at subsequent testing 35. The use of source animals free of PERV (none identified to date) or free of PERV-C could, in theory, prevent PERV transmission. Therefore, pigs with a null phenotype may or may not represent a reduced risk for PERV transmission; this remains to be tested in

vivo. Such phenotypic differences in PERV transmission is partly directed by genotypic differences in PERV integration patterns. The PERV integration pattern is highly polymorphic between various swine29,33,37. Pigs without active PERV loci may be found by genomic analyses in the future. In this regard, next generation sequencing technologies and the swine whole genome sequence 44 will be useful in addressing these issues.

To determine the transmission phenotype of pigs, PERV transmission methods were employed based on the co-cultivation of activated PBMC derived from candidate source animals with human or porcine cells31,35,38,43,45,46. These protocols are considered the 'gold standard' for analyzing the potential for PERV transmission. These assays are complex and time consuming, but no alternatives are currently available.

Xenograft recipients can be monitored for both circulating pig cells (a potential source of complication for assays termed "microchimerism") and for any potential PERV infection. It is notable in this regard that xenograft procedures to induce immunologic tolerance may involve intentional exposure to porcine hematopoietic cells ("mixed chimerism")47,48.

Prior PERV infection or exposure in recipients can be assessed using serologic assays seeking the presence of anti-PERV antibodies using an ELISA assay system19,49,50. Neutralization assays measuring virus-neutralizing antibodies in vitro may be more specific than Western blots7,51. However, in the absence of consistent control samples (i.e., to exclude exposure to pig cells or pig-derived products previously) the interpretation of such assays in regard to the presence of active infection may be difficult. Individual recipients may serve as their own controls for such assays; rising titers (usually at least four-fold) or an antibody class switch (IgM to IgG) may be taken as evidence of likely infection. Immunosuppressed patients may not generate timely serologic responses.

The most sensitive methods for PERV detection are PCR-based NAT. Use of accurate primer sets to identify PERV sub-types and the ability to distinguish true infection from contamination with porcine cellular material is essential. For PCR amplification, nucleic acids should be prepared from blood, sera, CSF and other bodily fluids. The use of validated, quantitative methods using human samples and with relevant controls and confirmed specificity and sensitivity measurements is paramount. Standard operating procedures should be provided to all participating laboratories, all equipment calibrated, and assays validated prior to initiating the trials. Methods should be able to detect <5 copies of DNA or RNA per 300,000 cells or 3ul of supernatant respectively7,18,19,49,52. The lessons learned from recent false positive nucleic acid assays from clinical samples (e.g., XMRV) suggest the importance of meticulous laboratory maintenance against contamination and assay error.

Surveillance and Search for Novel Pathogens

Familiar microbial agents account for many infectious syndromes in transplant recipients. Infection in such hosts is often asymptomatic. Thus, stored samples should be investigated for known pathogens at pre-established intervals as a basis for epidemiologic and safety studies. Etiologic agents causing disease in immunocompromised hosts are often unknown. With such uncertainty, investigators caring for xenograft recipients need to consider alternative approaches to surveillance and diagnosis in their immunocompromised xenograft recipients. This requires the routine collection and storage of frozen cells, serum samples, and tissue biopsies as well as donor sera and multiple tissue samples in advance of any adverse event. While these studies may be costly and considered as research investigations, possible approaches include:

• Use of broad-range molecular probes or polymerase chain reaction (PCR) primers which identify common genes (e.g., ribosomal genes such as 16S rRNA) shared within organism subclasses to recognize novel pathogens similar to those already known to cause disease in immunosuppressed hosts.

• Use of "chips" or microarrays carrying cDNAs for common classes of pathogens

• Developing additional molecular approaches for detecting novel genetic material (e.g., new DNA or mRNA species) present in recipients of xenograft tissues but not in normal individuals, including:

- Cloning of differences between two complex genomes (representational difference analysis, or RDA) can be used to isolate unusual mRNAs against a background of "normal" mRNAs. This technique was used to characterize pathogens such as Whipple's bacillus, hepatitis C and G viruses, and HHV8, the Kaposi's sarcoma-associated virus.

- Next generation sequencing or pyrosequencing: Allows sequencing of cDNA samples for detection of unknown pathogens. This may utilize specific genetic targets such as hypervariable regions within bacterial 16S rRNA genes amplified by PCR and then subjected to DNA pyrosequencing. A new arenavirus has been identified from allo-transplantation recipients by unbiased high-throughput sequencing26. Such approaches will enable clinical investigators and public health officials to begin to recognize and assess novel infections in xenotransplantation.

Routine monitoring for xenogeneic infection

In xenograft recipients the risks of infection and rejection necessitate lifelong monitoring. Monitoring schemes have been proposed to test for known pathogens and archive specimens from source animals, and from patients, intimate contacts, and animal handlers on a routine basis for use in the event of unexplained infectious episode (see also the Changsha Communiqué and FDA guidances13-15). Archived aliquots are likely to be required to be stored at least two separate locations. These samples may be utilized as further microbiologic assays are developed against previously unrecognized pathogens. Routine samples of sera and leukocytes might be studied for the emergence of human and pig-derived pathogens (PERV, PCMV, HCMV, EBV, PLHV) and co-cultivation of peripheral blood leukocytes with human and donor cell lines in the absence of clinical evidence of infection. In addition,

it may be recommended for patients to annually complete a questionnaire regarding their health status to monitor any developing syndromes or issues that need attention.

Assessment of the Xenograft Recipient with an Infectious Syndrome

The recipient presenting with fever, elevated or depressed leukocyte counts, hepatitis, pneumonia, signs of central nervous system infection, abscess or other focal infections, or xenograft dysfunction will have standard microbiological evaluations performed. This includes blood, urine, sputum, stool, and/or cerebrospinal fluid, chest radiography, biopsy or drainage of infected fluids in advance of any empiric antimicrobial therapy. Hospital admission and isolation may be required until the nature of the process is further defined. Special precautions (e.g., respiratory, secretions, neutropenia) will be dictated by the patients' clinical presentation. In the event of the recognition of a novel recombinant organism or severe infectious illness without explanation, strict isolation with HEPA filtration will be required. Empiric antimicrobial therapy should be provided based on the common causes of post-transplant infections.

If no etiologic agent or process can be established, special xenotransplant studies may be obtained on a regular basis (e.g., every three days) including co-cultivation of lymphocytes on human and porcine cells, viral cultures of serum on permissive human and porcine cells, nucleic acid testing for HCMV, PCMV, EBV, PLHV, HEV, porcine circovirus, PERV-A, -B, and -AC, human herpesvirus 6, and adenovirus. Specimens (serum, leukocytes) for archiving should also be obtained and processed. Any lesions (skin, tumors) should be biopsied for histopathology and cultures or nucleic acid testing.

Table 1: Categories of Potential Pathogens Resulting from Xenotransplantation (examples and availability of validated microbiological assays)
Common Human Pathogens of Allotransplant Recipients (EBV, CMV, herpes simplex virus, varicella zoster virus, Apergillus species, Listeria monocytogenes, mycobacterial species, Pneumocystis jirovecii) Specific microbiological assays are generally available
Traditional Zoonoses: well-characterized clinical syndromes of humans (*Toxoplasma gondii)* Specific microbiological assays are generally available
Species-specific agents: organisms *generally* thought to be incapable of causing infection outside the xenograft (e.g., porcine CMV) Some specific microbiological assays are available; few standardized assays available for use in humans
Potential pathogens: Organisms of broad "host range" which <u>may</u> spread beyond the xenograft (adenovirus) Some specific microbiological assays are available for use in humans; may not be standardized for porcine strains
Unknown pathogens: Organisms not known to be human pathogens, not known to be present in the source animals, or for which clinical syndromes and microbiologic assays are poorly described or unknown - New pathogenicity within the new host, while not known to be present or pathogenic (e.g., protozoa or retroviruses) - Viral recombinants resulting from intentional genetic modification of donor diseases resulting from multiple simultaneous infections

Table 2: Common Microorganisms of Swine to be Considered among Potential Causes of

Infection in Immunocompromised Swine and/or Human Xenograft Recipients*	
Bacteria	**Viruses**
Actinobacillus species (e.g., pleuropneumoniae)	Adenovirus sp.
Bordetella bronchoseptica	Encephalomyocarditis virus
Brucella suis	Influenza virus (swine, avian, human)
Campylobacter species (e.g., coli, jejuni)	Lymphocytic choriomeningitis virus (LCMV)
Chlamydia psittaci	Nipah (Hendra-like)
Clostridium difficile	Menangle virus
Corynebacterium species (i.e., pyogenes, suis)	Porcine circovirus
Haemophilus species (i.e., parasuis, suis)	Porcine cytomegalovirus (PCMV)
Klebsiella species (e.g., pneumoniae)	Porcine endogenous retrovirus (PERV)
Legionella pneumophila	Porcine hepatitis E virus
Leptospira species	Porcine lymphotropic herpesvirus (PLHV)
Listeria monocytogenes	Porcine parvovirus (PPV)
Mycobacterium species (i.e., bovis, tuberculosis, non-tuberculous mycobacteria)	Porcine Reproductive and Respiratory Syndrome virus
Mycoplasma hyopneumoniae (lung transplant)	Pseudorabies virus
Nocardia species	Rabies virus
Pasteurella species (i.e., haemolytica, multocida, pneumotropica)	Rotavirus
Pseudomonas species (i.e., aeruginosa, pseudomallei)	Torque teno virus
Salmonella species (i.e., typhi, typhimurium, cholerasuis)	**Fungi**
Serpulina hyodysenteriae	Aspergillus species
Shigella species	Candida species
Staphylococcus species (i.e., aureus, hyicus)	Cryptococcus species
Streptococcus species (e.g., pneumonia, suis)	Histoplasma capsulatum
Strongyloides species (e.g., ransomi)	Microsporum species
Yersinia species (i.e., enterocolitica, pseudotuberculosis)	Trichophytum species
Parasites	
Ascaris species	
Cryptosporidium species (i.e., parvum)	
Echinococcus	
Isospora species	
Neospora	
Strongyloides stercoralis	
Toxoplasma gondii	
Trichinella spiralis	

* Many porcine organisms have not been associated with human infection or disease but are included as being similar to organisms associated with human infection, infect human cells (e.g., PERV) in vitro, or are important causes of infection in immunocompromised swine or non-human primate recipients of porcine xenografts.

References

1. Bach FH, Fishman JA, Daniels N, et al. Uncertainty in xenotransplantation: individual benefit versus collective risk. Nat Med 1998;4:141-4.

2. Fishman JA. Xenosis and xenotransplantation: addressing the infectious risks posed by an emerging technology. Kidney Int Suppl 1997;58:S41-5.

3. Fishman JA. Infection and xenotransplantation. Developing strategies to minimize risk. Ann N Y Acad Sci 1998;862:52-66.

4. Fishman JA, Patience C. Xenotransplantation: infectious risk revisited. Am J Transplant 2004;4:1383-90.

5. Fishman JA. Infection in solid-organ transplant recipients. N Engl J Med 2007;357:2601-14.

6. Mattiuzzo G, Scobie L, Takeuchi Y. Strategies to enhance the safety profile of xenotransplantation: minimizing the risk of viral zoonoses. Curr Opin Organ Transplant 2008;13:184-8.

7. Mattiuzzo G, Takeuchi Y, Scobie L. Potential zoonotic infection of PERV in xenotransplantation. In: Rafael Manez Mendiluce CCV, ed. Xenotransplantation: Methods and Protocols. London, UK: Humana Press; 2011.

8. Mueller NJ, Takeuchi Y, Mattiuzzo G, Scobie L. Microbial safety in xenotransplantation. Curr Opin Organ Transplant 2011;16:201-6.

9. World Health Organization. WHA57.18 Human organ and tissue transplantation. 2004.

10. First World Health Organization Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials: Changsha, China, 19-21 November 2008. The Changsha Communique. Xenotransplantation;16:61-3.

11. U.S. Food and Drug Administration. PHS Guideline on Infectious Disease Issues in Xenotransplantation. 2001.

12. U.S. Food and Drug Administation. Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps). In; 2007.

13. U.S. Food and Drug Administration. Guidance For Industry: Public Health Issues Posed by the Use of Non-Human Primate Xenografts in Humans. In; 1999.

14. U.S. Food and Drug Administration. PHS Guideline on Infectious Disease Issues in Xenotransplantation. In; 2001.

15. U.S. Food and Drug Administration. Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans. In; 2003.

16. World Health Organization. WHO consultation on xenotransplantation – WHO/EMC/ZOO/98.1 (Guidance Document) 1997.

17. World Health Organization. OECD/WHO Consultation on Xenotransplantation Surveillance - WHO/CDS/CSR/EPH/2001.2 (Guidance Document). 2000.

18. Garkavenko O, Croxson MC, Irgang M, Karlas A, Denner J, Elliott RB. Monitoring for presence of potentially xenotic viruses in recipients of pig islet xenotransplantation. J Clin Microbiol 2004;42:5353-6.

19. Paradis K, Langford G, Long Z, et al. Search for cross-species transmission of porcine endogenous retrovirus in patients treated with living pig tissue. The XEN 111 Study Group. Science 1999;285:1236-41.

20. Heneine W, Tibell A, Switzer WM, et al. No evidence of infection with porcine endogenous retrovirus in recipients of porcine islet-cell xenografts. [erratum appears in Lancet 1998 Oct 31;352(9138):1478.]. Lancet 1998;352:695-9.

21. Patience C, Patton GS, Takeuchi Y, et al. No evidence of pig DNA or retroviral infection in patients with short-term extracorporeal connection to pig kidneys. [see comments.]. Lancet 1998;352:699-701.

22. OECD/WHO. OECD/WHO Consultation on Xenotransplantation Surveillance: Summary. 2001.

23. Humar A, Fishman JA. Donor-derived infection: old problem, new solutions? Am J Transplant 2008;8:1087-8.

24. Fishman JA, Strong DM, Kuehnert MJ. Organ and tissue safety workshop 2007: advances and challenges. Cell Tissue Bank 2009;10:271-80.

25. Fischer SA, Graham MB, Kuehnert MJ, et al. Transmission of lymphocytic choriomeningitis virus by organ transplantation. N Engl J Med 2006;354:2235-49.

26. Palacios G, Druce J, Du L, et al. A new arenavirus in a cluster of fatal transplant-associated diseases. N Engl J Med 2008;358:991-8.

27. Martin SI, Wilkinson R, Fishman JA. Genomic presence of recombinant porcine endogenous retrovirus in transmitting miniature swine. Virol J 2006;3:91.

28. Bartosch B, Weiss RA, Takeuchi Y. PCR-based cloning and immunocytological titration of infectious porcine endogenous retrovirus subgroup A and B. J Gen Virol 2002;83:2231-40.

29. Herring C, Quinn G, Bower R, et al. Mapping full-length porcine endogenous retroviruses in a large white pig. J Virol 2001;75:12252-65.

30. Takeuchi Y, Patience C, Magre S, et al. Host range and interference studies of three classes of pig endogenous retrovirus. J Virol 1998;72:9986-91.

31. Oldmixon BA, Wood JC, Ericsson TA, et al. Porcine endogenous retrovirus transmission characteristics of an inbred herd of miniature swine. J Virol 2002;76:3045-8.

32. Ericsson T, Oldmixon B, Blomberg J, Rosa M, Patience C, Andersson G. Identification of novel porcine endogenous betaretrovirus sequences in miniature swine. J Virol 2001;75:2765-70.

33. Niebert M, Tonjes RR. Analyses of prevalence and polymorphisms of six replication-competent and chromosomally assigned porcine endogenous retroviruses in individual pigs and pig subspecies. Virology 2003;313:427-34.

34. Akiyoshi DE, Denaro M, Zhu H, Greenstein JL, Banerjee P, Fishman JA. Identification of a full-length cDNA for an endogenous retrovirus of miniature swine. J Virol 1998;72:4503-7.

35. Wood JC, Quinn G, Suling KM, et al. Identification of exogenous forms of human-tropic porcine endogenous retrovirus in miniature Swine. J Virol 2004;78:2494-501.

36. Patience C, Switzer WM, Takeuchi Y, et al. Multiple groups of novel retroviral genomes in pigs and related species. J Virol 2001;75:2771-5.

37. Le Tissier P, Stoye JP, Takeuchi Y, Patience C, Weiss RA. Two sets of human-tropic pig retrovirus. Nature 1997;389:681-2.

38. Wilson CA, Wong S, Muller J, Davidson CE, Rose TM, Burd P. Type C retrovirus released from porcine primary peripheral blood mononuclear cells infects human cells. J Virol 1998;72:3082-7.

39. Bartosch B, Stefanidis D, Myers R, Weiss R, Patience C, Takeuchi Y. Evidence and consequence of porcine endogenous retrovirus recombination. J Virol 2004;78:13880-90.

40. Scobie L, Taylor S, Wood JC, et al. Absence of replication-competent human-tropic porcine endogenous retroviruses in the germ line DNA of inbred miniature Swine. J Virol 2004;78:2502-9.

41. Wilhelm M, Fishman JA, Pontikis R, Aubertin AM, Wilhelm FX. Susceptibility of recombinant porcine endogenous retrovirus reverse transcriptase to nucleoside and non-nucleoside inhibitors. Cell Mol Life Sci 2002;59:2184-90.

42. Qari SH, Magre S, Garcia-Lerma JG, et al. Susceptibility of the porcine endogenous retrovirus to reverse transcriptase and protease inhibitors. J Virol 2001;75:1048-53.

43. Hector RD, Meikle S, Grant L, Wilkinson RA, Fishman JA, Scobie L. Pre-screening of miniature swine may reduce the risk of transmitting human tropic recombinant porcine endogenous retroviruses. Xenotransplantation 2007;14:222-6.

44. Archibald AL, Bolund L, Churcher C, et al. Pig genome sequence--analysis and publication strategy. BMC genomics 2010;11:438.

45. Garkavenko O, Wynyard S, Nathu D, et al. Porcine endogenous retrovirus transmission characteristics from a designated pathogen-free herd. Transplant Proc 2008;40:590-3.

46. Garkavenko O, Wynyard S, Nathu D, et al. Porcine endogenous retrovirus (PERV) and its transmission characteristics: a study of the New Zealand designated pathogen-free herd. Cell Transplant 2008;17:1381-8.

47. Sachs DH. Mixed chimerism as an approach to transplantation tolerance. Clinical Immunology 2000;95:S63-8.

48. Issa NC, Wilkinson RA, Griesemer A, et al. Absence of replication of porcine endogenous retrovirus and porcine lymphotropic herpesvirus type 1 with prolonged pig cell microchimerism after pig-to-baboon xenotransplantation. J Virol 2008;82:12441-8.

49. Niebert M, Tonjes RR. Molecular cloning and functional characterization of infectious PERV and development of diagnostic tests. Curr Top Microbiol Immunol 2003;278:217-37.

50. Tacke SJ, Bodusch K, Berg A, Denner J. Sensitive and specific immunological detection methods for porcine endogenous retroviruses applicable to experimental and clinical xenotransplantation. Xenotransplantation 2001;8:125-35.

51. Matthews AL, Brown J, Switzer W, Folks TM, Heneine W, Sandstrom PA. Development and validation of a Western immunoblot assay for detection of antibodies to porcine endogenous retrovirus. Transplantation 1999;67:939-43.

52. Garkavenko O, Obriadina A, Meng J, et al. Detection and characterisation of swine hepatitis E virus in New Zealand. J Med Virol 2001;65:525-9.

Annex 5

Second Global Consultation on Regulatory Requirements for Xenotransplantation Clinical Trials

Organized in collaboration with the International Xenotransplantation Association and The Transplantation Society
17-19 October 2011, Geneva, Room M 505

Agenda

17 October

09:30	Welcome	Luc Noel Emanuele Cozzi
09:40	Introduction of participants Election of Chair and Rapporteurs	
10:00	From Changsha to the objectives of the second consultation	Luc Noel
10:15	Discussion	
10:30	*Coffee Break*	

Update on progress in the last three years

11:00	Basic science	Léo Bühler
11:15	New potential use for xenotransplantation	Emanuele Cozzi
11:30	Infectious risks	Jay Fishman
11:50	The experience of WHO Global Alert and Response	Thomas Grein
12:10	The International Health Regulation in practice	Bruce Plotkin
12:30	*Lunch break*	

Breakout groups

13:30- 15:30	-1) Scenario and response to anticipate the infectious risk: -2) Optimizing and standardizing testing and identification of xenotransplantation associated infection -3) Revisiting and prioritizing essential requirements for clinical trials
15:30	*Coffee Break*
16:00	Groups report and discussion
17:00	Managing the infectious risk and guidance for post-xenotransplantation management and diagnosis General discussion led by Jay Fishman
18:00	*Close for the day*

18 October

9:00	Summary by Rapporteurs	

The oversight of xenotransplantation clinical trial

10:00	Medsafe	Stewart Jessamine
10:30	FDA	Keith Wonnacott
11:00	*Coffee break*	
11:30	Discussion	
12:30- 13:30	*Lunch break*	

Round table review of xenotransplantation activities in countries

14:00	
15:00	*Coffee Break*
15:30	
18:00	*Close for the day*

19 October

9:00	Summary by Rapporteurs
9:30	WHO Aide Mémoire on minimizing risks in xenotransplantation Discussion
10:30	*Coffee break*
11:00	The way forward and next steps
12:00	Conclusion
12:30	*Closure of the meeting*

Annex 6

List of Participants

Dr Léo H. BÜHLER
Unité d'Investigations chirurgicales
Hôpitaux Universitaires Genève
Rue Micheli-du-Crest 24
CH-1211 Genève 14
Leo.Buhler@hcuge.ch

Myra CHENG
PhD Candidate
Faculty of Law
University of Technology, Sydney
PO Box 123
Broadway NSW 2007
Australia
myra.cheng@uts.edu.au

Dr Peter COWAN
Immunology Research Centre
St Vincents Hospital
41 Victoria Parade
Fitzoy
VIC 3065
Australia
peter.cowan@svhm.org.au

Dr Emanuele COZZI
Unit Director
Clinical and Experimental Transplantation Immunology
Department of Medical and Surgical Sciences
University of Padua - Ospedale Giustinianeo
Via Giustiniani, 2
I-Padova
Italy
emanuele.cozzi@unipd.it

Dr Elvira DEL PRETE
Wissenschaftliche Mitarbeiterin
Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Öffentliche Gesundheit
Seilerstrasse 8
CH-3003 Bern
elvira.delprete@bag.admin.ch

Dr Shaoping DENG (unable to attend)
Assistant Professor of Surgery
Massachusetts General Hospital
CPZN-4-4702 & Thier 8
55 Fruit St
Boston, MA 02114, USA
sdeng1@partners.org

Dr Jay A. FISHMAN
Director, Transplant Infectious Disease & Compromised Host Program
Massachusetts General Hospital
Infectious Diseases Division
Harvard Medical School
55 Fruit Street, GRJ504
Boston, MA 02114, USA
jfishman@partners.org

Dr Bernhard HERING
Professor of Surgery and Medicine
Department of Surgery
Medicial School
420 Delaware St. S.E., MMC 280
Minneapolis MN 55455, USA
bhering@umn.edu

Dr Stewart JESSAMINE
Group Manager, Medsafe
Ministry of Health
Level 6, Deloitte House
16 Brandon Street
PO Box 5013
Wellington
New Zealand
stewart_jessamine@moh.govt.nz

Dr Uladzimir KHRYSHCHANOVICH
2nd Department of Surgical Diseases
Belarusian State Medical University
83 Dzerzhinskogo pr.
220116
Minsk
Belarus
vladimirkh77@mail.ru

Dr Sang Joon KIM
Professor of Surgery
Seoul National University College of Medicine
Director, Xenotransplantation Research Centre
101 Daehak-ro
Jongno-gu
Seoul 110-744
Republic of Korea
sjkimgs@plaza.snu.ac.kr

Dr Takaaki KOBAYASHI
Department of Applied Immunology
(Department of Surgery II)
Nagoya University School of Medicine
65 Tsurumai-cho
Showa-ku
Nagoya, 466-8550
Japan
takakoba@med.nagoya-u.ac.jp

Professor Ivo KWON
Bioethics Policy Research Center
No. 316 Law B/D 11-1 Daehyun-dong
Seodaemun-Gu
Seoul 120-750
Republic of Korea
kivo@ewha.ac.kr

Dr Enrique MARTINEZ GUTIERREZ
Director del Registro Nacional de
Trasplantes,
Centro Nacional de Trasplantes
Carretera Picacho Ajusco, No 154 6to Piso
Co. Jardines en la Montaña, Del. Tlalpan
C.P. 14210 Mexico D.F.
Mexico
enrique.martinez@cenatra.org
enrique.martinez@salud.gob.mx

Dr Cláudio NISHIZAWA
Regulation and Health Surveillance Specialist
Research and Clinical Trials Office
National Health Surveillance Agency
Agência Nacional de Vigilância Sanitária
SIA Trecho 5, Area Especial 57
Brasília
DF 71205-050
Brazil
Claudio.Nishizawa@anvisa.gov.br

Dr Olga ORLOVA
Chief of the Research Organization and Development Department
Federal Research Center of Transplantology and Bioartificial Organs named after Academician V. Shumakov
Ministry of Health and Social Development of Russia
123182 Schukinskaya 1
Moscow
Russian Federation
orlovaolgav@mail.ru

Dr Chung-Gyu PARK
Associate Dean for Research Affairs
Department of Microbiology and Immunology
Cancer Research Institute
Xenotransplantation Research Center
Seoul National University College of Medicine
103 Daehak-ro Jongno-gu
110-799 Seoul
Republic of Korea
chgpark@snu.ac.kr

Professor Richard PIERSON
International Xenotransplantation Association
Univerity of Maryland
Dept. Cardiac Surgery N4W94
22 South Greene St.
Baltimore, MD 21201
USA
rpierson@smail.umaryland.edu

Dr Linda SCOBIE
Glasgow Caledonian University
City Campus
70 Cowcaddens Rd
Glasgow
G4 0BA
Scotland
linda.scobie@gcu.ac.uk

Dr Glenn SMITH
Blood and Tissue Unit
Therapeutic Goods Administration
P.O. Box 100
Woden ACT 2606
Australia
glenn.smith@tga.gov.au

Dr Yasu TAKEUCHI
Research Department of Infection
Wohl Virion Centre
Cruciform Building, Rm 1.3.11
Gower St.
London
WC1E 6BT
U.K.
y.takeuchi@ucl.ac.uk

Dr Ralf R. TÖNJES
Paul-Ehrlich-Institute
Federal Agency for Sera and Vaccines
Division of Medical Biotechnology
Section 6/4, "Non-Vital Tissue Preparations, Xenogeneic Cell Therapeutics"
Paul-Ehrlich-Strasse 51-59
D-63225 Langen, 1Germany
Ralf.Toenjes@pei.de

Professor Wei WANG
Director, Cell Transplantation and Gene Therapy Institute
Third Xiang-Ya Hospital of Central-South University
Tongzipo Road
Yuelo District
Changsha
Hunan 410013
People's Republic of China
wawe01cn@yahoo.com.cn

Dr Keith WONNACOTT
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration (FDA)
1401 Rockville Pike
Rockville, MD 20852, USA
keith.wonnacott@fda.hhs.gov

WHO Secretariat

Ms Mar CARMONA
Technical Officer
Clinical Procedures, Health System Governance and Service Delivery
Health Systems and Services, World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland

Ms Fiona CONSTABLE
Assistant to Dr Luc Noël
Clinical Procedures, Health System Governance and Service Delivery
Health Systems and Services, World Health Organization
20 avenue Appia, CH-1211 Geneva 27, Switzerland
constablef@who.int

Dr Thomas GREIN
Coordinator, Alert and Response Operations
Health Security and the Environment
World Health Organization
20 avenue Appia
CH-1211 Geneva 27,
Switzerlandgreint@who.int

Dr Luc NOËL
Coordinator, Clinical Procedures,
Health System Governance and Service Delivery
Health Systems and Services, World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland
noell@who.int

Dr Bruce PLOTKIN
Technical Officer (Legal)
IHR, Regulations, Procedures and Information
Health Security and the Environment
World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland
plotkinb@who.int

Dr Sunil SENANAYAKE
Regional Adviser
National Health Policy and Health Financing (NPF)
Department of Health Systems Development (HSD)
Regional Office for South-East Asia
World Health Organization
New Delhi
India
senanayakes@searo.who.int

Dr Willem VAN LERBERGHE
Director, Health System Governance and Service Delivery
Health Systems and Services, World Health Organization
20 avenue Appia
CH-1211 Geneva 27, Switzerland
vanlerberghew@who.int

WHO/HTP/EHT/CPR/2011.01