Overview of Regulatory Guidelines for Xenotransplantation
Osaka, November 2013

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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 policy-making 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.

REFERENCE

Xenotransplantation Advisory Consultation
organized by Dr L. Noel, (WHO), Geneva April 2005

- Launch of an international human xenotransplantation inventory

- World Health Organization

International Xenotransplantation Association (IXA)

Geneva University Hospital
Inventory of Human Xenotransplantation practices
AIMS:

- To collect basic data on all types of human xenotransplantation practices performed since 1995

- To identify countries where such practices exist to provide information for international agencies, national health authorities, health care workers and the public

- To encourage good practices, international guidelines and regulation and foster a better perception of hopes and risks in xenotransplantation
METHODS:

- Scientific publications
- Presentation at International Congresses
- Internet
- Reports by members of the transplantation community
- Electronic questionnaire available on the website
RESULTS:
Since October 2006

Hits = mean = 3000 /month

<table>
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<tr>
<th>No</th>
<th>Tissue/Animal/Country</th>
<th>Consult</th>
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<tbody>
<tr>
<td>1</td>
<td>Kidney cells</td>
<td>Hamster</td>
</tr>
<tr>
<td>2</td>
<td>Adult cells</td>
<td>Sheep</td>
</tr>
<tr>
<td>3</td>
<td>Chromaffin cells</td>
<td>Calf</td>
</tr>
<tr>
<td>4</td>
<td>Fetal ventral mesencephalic cell</td>
<td>Pig</td>
</tr>
<tr>
<td>5</td>
<td>Stem cells</td>
<td>rabbit, pig</td>
</tr>
<tr>
<td>6</td>
<td>Embryonic stem cells</td>
<td>blue shark</td>
</tr>
<tr>
<td>7</td>
<td>Embryonic stem cells</td>
<td>Pig</td>
</tr>
<tr>
<td>8</td>
<td>Embryonic stem cells</td>
<td>Pig</td>
</tr>
<tr>
<td>9</td>
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</tr>
<tr>
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<td>Embryonic stem cells</td>
<td>- fetal cells, adult cells</td>
</tr>
<tr>
<td>11</td>
<td>Fetal islet like cell clusters</td>
<td>Pig</td>
</tr>
<tr>
<td>12</td>
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</tr>
<tr>
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<tr>
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<td>Hepatocytes</td>
<td>Pig</td>
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<tr>
<td>18</td>
<td>Islets of Langerhans</td>
<td>Rabbit</td>
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<td>- Sertoli cells</td>
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</table>

\[ N = 32 \]
International Human Xenotransplantation Inventory

Antonino Sgroi,1 Leo H. Bühlner,1 Philippe Morel,1 Megan Sykes,2 and Luc Noel3,4

Background. Xenotransplantation carries inherent risks of infectious disease transmission to the recipient and even to society at large, and it should only be carried out with strict regulation and oversight. In collaboration with the International Xenotransplantation Association, the University Hospital Geneva, and the World Health Organization, an international inventory has been established (www.humanxenotransplant.org) aiming to collect basic data on all types of currently ongoing or recently performed xenotransplantation procedures in humans.

Methods. We collected information from publications in scientific journals, presentations at international conferences, and from a network of experts in the field.
1st Global Consultation on Regulatory Requirements for Clinical Trials of Xenotransplantation
Changsha, China, November 2008

In collaboration with the Chinese Ministry of Health, the University of Changsha and the International Xenotransplantation Association (IXA)

Topics
• Xenogeneic transplantation only when effective national regulatory control and surveillance mechanisms are in place
• Human clinical trials, in particular of porcine pancreas islets
• Xenotransplant tourism
• The meeting brought together experts with representatives of health authorities from all regions of WHO.
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.

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1 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.
WHO, Changsha Communiqué

- Principle 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.
WHO, Changsha Communiqué (contd.)

- **Principle 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.
WHO, Changsha Communiqué (contd.)

- Principle 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.
2nd Global Consultation on Regulatory Requirements for Clinical Trials of Xenotransplantation

Geneva, Switzerland, October 2011

In collaboration with the International Xenotransplantation Association (IXA) and the Transplantation Society (TTS)

The charge to the consultation was

• To review the current status of xenotransplantation science and practice
• 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
• To discuss and refine draft guidance for infectious disease surveillance, prevention, and response appropriate to support various probable clinical xenotransplantation trial scenarios.
Original Article

Xenotransplantation-associated infectious risk: a WHO consultation


Abstract: Xenotransplantation carries the potential risk of the transmission of infection with the cells or tissues of the graft. 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. 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. Xenotransplantation will necessitate the development of surveillance programs to detect known infectious agents and, potentially, previously unknown or unexpected pathogens. The development of surveillance and safety programs for clinical trials in xenotransplantation is guided by a “Precautionary Principle,” with the deployment of appropriate screening procedures and assays for source animals and xenograft recipients even in the absence of data suggesting infectious risk.