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Regulating Clinical Xenotransplantation in Europe

Annika Tibell

Xenotransplantation has raised considerable concern since there is a risk that animal-derived micro-biological agents may spread via a patient into the community, thereby possibly introducing new infectious diseases into the human population. As a result, many countries and international organizations have taken the stand that clinical xenotransplantation research requires a special regulatory network.

Regulation relating to xenotransplantation covers a much broader area than ruling on the initiation of clinical trials. It may also include the regulation of experimental studies, animal protection laws, various laws regulating the creation of transgenic animals, the import and export of source animals or xenografts, environmental and public health protection, infectious disease control, and laws related to indemnity, responsibility and compensation rights. This brief survey focuses on regulation and guidelines directly concerning the initiation of clinical trials.

To monitor the legal and regulatory developments in Europe, the European Council's Working Party on Xenotransplantation distributed a questionnaire at the end of 1999. Only 3 of the 18 European countries responding to the survey, namely France, the Netherlands and Switzerland, had legislation covering clinical xenotransplantation. Several others have developed advisory guidelines or are preparing guidelines or legislation.

The Status of Xenotransplantation in Certain European Countries

United Kingdom (UK). Two important reports on xenotransplantation have been published in the UK.^{1,2} Both recommended the creation of a special

authority to deal with cross-species transplantation. In 1997, the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) was set up. With support from expert assessors, the UKXIRA will advise ministers on individual applications for human trials and on developments in the field. UKXIRA has published a document describing the application procedure and the decision-making process.³ The application will also be assessed by other authorities involved, such as the Medicines Control Agency or the Medical Devices Agency. The final decision whether to approve a clinical trial or not will be made by the Minister of Health. The trial must also be approved by the local research ethics committee. The UKXIRA has also prepared several reports about infectious issues that are available via their website (www.open.gov.uk/doh/ukxira.htm).

France. In 1998, the French parliament approved a statutory reform in the health care area. The new law specifically states that therapeutic use of cells, tissues or organs derived from animals should follow the rules for biomedical research. A clinical xenotransplantation trial must be approved by the Minister of Health after being considered by both the government's transplantation agency, *Établissement Français des Greffes*, and a new health protection authority. An expert group on xenotransplantation was established within *Établissement Français des Greffes* in 1995, and a report on the issue was published in 1998.⁴

Spain. In 1997, a committee of experts was formed to follow developments in the field, consider applications for clinical trials, and set up a register of xenograft recipients. In June 1998, the committee published guidelines for xenotransplantation.⁵

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So far, the European Union has taken no legislative initiative in the field of xenotransplantation, but regulations concerning medicinal products may be applicable in certain fields of cellular xenografting.

These guidelines require 6 months' function of a xenograft without signs of transferral of infectious agents in a relevant experimental model before a clinical trial can be considered. If transferral of an infectious agent occurs, a minimum 12-months follow-up period without signs of infection is required. Informed consent should be obtained from the patients and their close contacts.

Germany. At present, there is no special legislation relating to trials of clinical xenotransplantation in Germany. Advisory guidelines are being prepared by the German Medical Association (Bundesärztekammer).

The Netherlands. In 1997, a committee was formed to evaluate the present scientific status of xenotransplantation. Its report underlines the considerable uncertainty that remains regarding many aspects of this technology. Questions remain regarding the success and clinical applicability of techniques to inhibit the immune response, the adequate function of animal tissue in humans, and the risk of transfer of microbiological agents from animals to humans.⁶ The report underlines the fact that xenotransplantation is still at an early stage of development, but considers that, if the technique becomes clinically viable, it is ethically acceptable. At present, proposals for certain kinds of clinical studies, including xenotransplantation, have to be assessed by a central committee. However, a legally-binding moratorium on trials of xenotransplantation in humans is being drafted.

Switzerland. A Swiss report on xenotransplantation was published in 1998, and a report focused on cellular xenografting is planned for the fall of 2000.⁷ The present transplantation law includes xenotransplantation. Clinical trials require special permission. More detailed regulations are being drafted.

The Nordic Countries. In Sweden, the government's xenotransplantation committee presented its report, "From one species to another—transplantation from animals to humans", in 1999.⁸ The statutory proposals include the creation of a central authority, a register of xenograft recipients, and a tissue bank for samples from recipients and source animals. The initiation of a clinical trial would require approval by a central xenotransplantation authority as well as approval by human and animal research ethics committees. The report has been distributed

for comments and will be submitted to the parliament in spring 2001.

Norway has recently appointed a xenotransplantation committee. While awaiting its report, a 3-year moratorium for clinical xenotransplantation research has been declared. The other Nordic countries, Denmark, Finland and Iceland, have taken no legislative measures.

Activities in the European Union and European Council

So far, the European Union has taken no legislative initiative in the field of xenotransplantation, but regulations concerning medicinal products may be applicable in certain fields of cellular xenografting. The concept of xenotransplantation has also been discussed in the European Group on Ethics in Science and New Technologies.

More activities are in progress in the European Council. In 1998, the parliament called for a European moratorium on clinical xenotransplantation research. The issue was dealt with by the ministers, who instead set up a Working Party on Xenotransplantation under the joint responsibility of the Steering Committee on Bioethics and the European Health Committee. The committee is drafting guidelines for clinical xenotransplantation research. As pointed out by many reports in the field, infections do not respect geographical frontiers so there is a need for international collaboration and harmonization of regulations. The work in the European Council is followed by observers from the European Union, the Food and Drug Administration (FDA) in the USA, from Health Canada, from the Organization for Economic Co-operation and Development (OECD), from the Office International des Épizooties (OIE), and from the World Health Organization (WHO). The International Xenotransplantation Association has observer status. The need for a global perspective, especially concerning infectious disease issues and ethics, has also been discussed previously at meetings organized by the FDA, WHO and OECD.

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