

Xenotransplantation: A European Perspective

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Summary — A transnational approach is clearly the best way for the ethical and public health issues surrounding xenotransplantation to be discussed and coordinated policies formulated. However, the inertia involved in such processes, at a time of developments in the research underpinning xenotransplantation, conspire to ensure that there is always likely to be a lag between technical progress and regulatory developments. Although individual regions and nations are under pressure to address some of these issues, local and regional policy development must not lose sight of the need for a global strategy.

Key words: *animal research, Europe, regulation, xenotransplantation.*

Introduction

This paper explores recent and current developments relating to the regulation of xenotransplantation at the European level. The views expressed are those of the author and are not presented as, nor should they be mistaken for, necessarily being the views of the Government of the UK.

Novel xenotransplantation procedures raise important issues, primarily related to ethics and public health, above and beyond those normally encountered when novel healthcare technologies are developed and introduced (1–3). These issues require constructive general public discussion, informed by scientific evidence and ethical insights, so that the political debate that will guide government policies will reflect consensus views derived from a clear understanding of public opinion and the ethical issues and scientific evidence. In addition, there are potential global public health and other considerations that require a coordinated transnational approach.

It is important to remember that xenotransplantation does not relate only to solid organ transplants. The commonly used definition (4) includes the implantation of animal cells and human materials that have been co-cultured with animal cells. It is sometimes forgotten that this wider definition embraces some technologies that have already been established in clinical practice (for example, as part of assisted reproduction programmes [5] or skin substitutes).

There are two main arguments that are typically advanced in support of xenotransplantation technologies. First, if safety and efficacy can be established, xenotransplantation of solid organs from animals to humans could help overcome the chronic lack of suitable human donor organs. Second, other xenotransplantation technologies might make possible clinical advances not feasible by other contemporary therapeutic strategies.

The case against the indiscriminate (and even the controlled) development and introduction of xenotransplantation procedures revolves around unresolved ethical concerns about the use of animals, the associated animal welfare costs, and potential, but as yet unquantifiable, infective and other risks to the patient, his or her close contacts, and the wider population.

This paper focuses on how progress with some of these issues is being made within Europe.

The Council of Europe

The Council of Europe is a confederation of more than forty Member States committed to the development, promulgation and adoption of measures intended to promote shared cultural and societal values.

Although those who sign and ratify its outputs are committed to their implementation, in the case of European Union Member States, they are not, unless also ratified by the European Commission, required to incorporate the outputs into domestic law.

In 1997, the Committee of Ministers of the Council of Europe adopted a recommendation (*R [97] 15*) (see 6) proposing that the Member States of the Council of Europe should devise and establish mechanisms for the registration and regulation of aspects of xenotransplantation. The recommendation covered basic research, clinical trials and the use of xenotransplantation procedures in clinical practice. It also made provision for the long-term follow-up of xenotransplant recipients and for the welfare of the source animals.

In 1999, the Parliamentary Assembly of the Council of Europe adopted *Recommendation 1399* (1999; see 6), calling for a moratorium on all human xenotransplantation trials and practices.

In response, the Committee of Ministers, without taking a stance on the proposed moratorium, estab-

lished a Working Party to address the concerns raised by the Parliamentary Assembly (see 6). In particular, it sought advice on safety, efficacy and animal welfare issues, and it acknowledged that the nature of the issues required the involvement of other transnational agencies.

The multidisciplinary Working Party was jointly managed by the Steering Committee on Bioethics (CDBI) and the European Health Committee (CDSF) of the Council of Europe. It involved those from relevant medical disciplines and those with knowledge of research, the law, ethics and animal welfare.

The terms of reference of the Working Party included:

- to monitor developments . . . in cooperation with other international organisations;
- to collect and make information available;
- to prepare and publish periodical reports on the state-of-the-art; and
- to consider ethical/legal principles; issues relating to safety, efficacy, efficiency and animal welfare; to make recommendations for informing others; and to prepare draft guidelines on xenotransplantation.

The key outputs were expected to be statements on the scientific basis for and risks likely to be associated with xenotransplantation and a non-binding draft recommendation on the development, regulation and implementation of xenotransplantation technologies.

These original terms of reference expired 31 December 2001.

At the time of writing, interim and draft reports on the state-of-the-art of xenotransplantation have been produced (see 6), but the recommendation on the regulation of xenotransplantation is unfinished.

These outputs, such as they are, seem generally consistent with material being produced on the subject of xenotransplantation by the European Commission, OECD (7), and the World Health Organization (8).

The United Kingdom

In the meantime, individual national authorities, faced with an immediate need to deal with developments in xenotransplantation, have sought to devise and implement appropriate national measures pending the development and agreement of a coordinated transnational position.

In 1995, the UK Government commissioned an independent Advisory Group on the Ethics of Xenotransplantation to advise on these issues.

The product of this Advisory Group was the Kennedy Report, *The Ethics of Xenotransplantation: Animal Tissues Into Humans*, published in 1997 (1). The report dealt primarily with issues related to science rather than ethics, but it nevertheless made a number of important points in its sixty or more recommendations.

Key concepts emerging from the report include the insight that the ethical considerations of the issues surrounding xenotransplantation must be continuous and must be revisited as new information becomes available; and that providing certain safety and efficacy concerns can be satisfactorily resolved, the use of pigs as source animals might be ethically acceptable, but that non-human primates should not be used as source animals for clinical applications.

These principles provide the basis for current Government policy in the UK. There is a strong presumption against the use of organs from non-human primates. The use of pigs as source animals may be considered, providing issues relating to safety, efficacy and animal welfare are properly addressed and matters related to privacy, consent and clinical surveillance are taken into account.

The Kennedy Report also recommended the establishment of a regulatory body to oversee the development of clinical xenotransplantation in the UK.

In 1997, the Government established the UK Xenotransplantation Interim Regulatory Authority (UKXIRA; see 4) with these terms of reference:

To advise . . . on action necessary on xenotransplantation, taking into account the principles outlined in the Kennedy Report, and worldwide developments in xenotransplantation. In particular to advise:

- a) on safety, efficacy and considerations of animal welfare in liaison with the Home Office, and any other pre-conditions for xenotransplantation for human use, and whether these have been met;
- b) on research required to assess safety and efficacy factors in xenotransplantation procedures;
- c) on the acceptability of specific applications to proceed with xenotransplantation in humans; and
- d) to provide a focal point on xenotransplantation issues within Government.

Transparency is achieved through the publication of minutes of meetings, annual open meetings and annual reports, and the publication of technical reports and other guidance. Publications to date

provide guidance on making proposals for xenotransplantation involving human subjects and various biosecurity issues (see 4).

Loose Ends

Despite all of the activity described above, a number of important issues have yet to be fully debated and resolved.

Notwithstanding some strong early declarations that the use of non-human primates as source animals for solid organs for clinical use was not acceptable, the language used in more recent European documents suggests that their use might not be completely ruled out.

The existing European national regulatory frameworks relating to pre-clinical and clinical xenotransplantation systems remain many and varied. Clinical or pre-clinical xenotransplantation is believed to be under way, or under discussion, in several countries, with animal-based studies taking place in a dozen or more.

Whilst the need for a transnational approach is evident, the inertia involved in working at that level may inevitably result in regulations always lagging behind other developments.

The precautionary principle is commonly cited as a key consideration. Further work is required to enable the associated risks to be identified, assessed, minimised and managed. However, it is unlikely that they will be eliminated. There is still no definitive guidance on the performance and

safety criteria to be met before a clinical trial of solid organ transplantation into humans might be considered.

Equally important, many feel that the best forum for these issues to be discussed and resolved has yet to be defined.

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