

Scott Parker
is an assistant solicitor
at Simmons & Simmons,
and a member of the
firms pharmaceutical
and medical group.

Cell therapy: European legal and regulatory implications

Date received (in revised form): 21st June, 2001

Scott Parker

Abstract This paper reviews some of the legal and regulatory considerations that may arise in connection with the use in Europe of cell therapy approaches for the treatment of disease.

Keywords: legal, regulatory, ethical, cell, therapy, consent

Introduction

Cell therapy is the administration to humans of living cells of autologous (from the patient under treatment), allogeneic (from another human being) or xenogeneic (from an animal) origin that have been manipulated or processed *ex vivo* in order to alter their biological characteristics. Cell therapy may have therapeutic, diagnostic or preventative applications and a range of cell therapy approaches are currently being evaluated for treatment of cancer and a large number of autoimmune and genetic disorders.

There are no European laws or regulations dealing specifically with cell therapy. Instead this diffuse and predominantly novel range of therapies comes under the control of a number of existing regulatory regimes. The purpose of this paper is to review the legal considerations arising and to identify the regulatory framework that will apply to different cell therapy strategies in Europe, with a particular focus on the UK.

General legal considerations

Cell therapy, and in particular allogeneic cell therapy where a product derived from one individual's cells is used to treat others,

raises a number of legal issues. Any cell therapy strategy, other than xenogeneic therapies, will require that prior to the therapy itself cells must be taken from a human being (who may be either the intended patient or an unrelated individual). In the absence of any European legislation, the national laws governing the taking of human tissue must be considered.

In the UK there is no statute law of general application that deals with the removal, transplantation, or use of cells or tissues in the course of medical treatment or for scientific research. However, where such cells or tissue are taken from the dead or where such is covered by the Human Organ Transplant Act 1989 or the Human Fertilisation and Embryology Act 1990 the removal of tissue will be regulated by statute. Thus the taking of cells from an individual for cell therapy purposes is not generally governed by statute but will instead have to satisfy the common law justification that to do so is in the public interest and does not offend public decency as interpreted by the courts. Of course the removal of human tissue for research purposes should be considered in the context of the basic legal principle that unconsented interference with the body of another is unlawful. For a full analysis of the

Scott Parker
Solicitor, Intellectual
Property Group,
Simmons & Simmons,
21 Wilson Street,
London
EC2M 2TX, UK
Tel: +44 (0)208 975 2082
E-mail:
Scott.f.parker@sb.com

framework of ethical principles governing the use of human tissue outside the donor's body, including a detailed analysis of consent, the reader is referred to the Nuffield Council on Bioethics (NCB) 1995 report on 'Human Tissue: Ethical and Legal Issues'.

There remains some uncertainty as to whether human cells are to be considered as 'property' in the legal sense and as to the effect of consenting to the removal of tissue. Accordingly, it is necessary to address the way in which human cells may be used once taken from the individual and whether the donor may have any claims over the cell therapy product itself or any profits deriving from the exploitation thereof.

In the well-known US case of Moore¹ it was held that the plaintiff had no property rights in products developed from tissue taken from his body. Importantly, the court did not rule on whether a claim could be framed on the basis that the plaintiff had not consented to his tissue being used in the way that it was. In the UK it is unlikely that any claim would succeed on the basis that tissue is property over which the donor can claim an interest. The question of whether consent to removal of tissue constitutes an abandonment of all rights in the tissue regardless of the use to which the tissue is put is, however, a more difficult one. The NCB has recommended that any consent to removal of tissue given by a patient in the course of medical treatment should be taken to include consent to any further acceptable use and that tissue removed in the course of treatment (with consent) should be regarded as being free of all claims provided that subsequent use is in accordance with appropriate ethical, legal and professional standards. The Medical Research Council (MRC) has, however, advised that whenever practicable and in all instances where it may be possible to trace back the results of research to an individual patient whose interests may be affected, informed consent should be obtained in relation to the subsequent use for research purposes of surplus material. Where surplus material is only to be used for anonymised unlinked research the MRC has advised that such consent is not necessary.

The approach to consent set out in the preceding paragraph will be of relevance not only to autologous donors but also to certain allogeneic donors, where tissue is taken with consent during the course of medical treatment (ie where a tumour is excised in the course of treatment and subsequently used to generate an allogeneic cell therapy product). It should be noted, however, that a stricter regime should apply where tissue is not taken as part of a therapeutic process.

Where tissue is voluntarily donated (ie other than in the course of treatment) more rigorous safeguards are appropriate. In such circumstances the NCB has recommended that such tissue be regarded as a gift and that the use to which such tissue may subsequently be put would depend on the terms of the consent given. If tissue is taken voluntarily but is intended to be kept for future use as an autologous cell therapy product then the use to which the cells may be put and the donor's rights over such cells would depend on the terms of the agreement under which such cells are to be kept.

Until such time as these issues are satisfactorily resolved so as to give certainty it remains a possibility that legal claims could be brought by donors on the basis of the absence of consent to a particular use. Accordingly, an appropriate consent should be sought, not least because it is universally accepted that clinical trials of any cell therapy approach will require research ethics committee approval.

The consent sought should be explicit, given on the basis of all appropriate information and should cover not only the removal of the tissue but also the subsequent use thereof. Indeed, the Biotechnology Patent Directive recommends that in relation to patent applications for inventions based on biological material of human origin 'free and informed consent thereto' should be given (although it should be noted that no such provision is included in the implementing legislation in the UK).² In the UK the MRC has recommended that when seeking consent to take human tissue for research a two-part consent process should be followed where the donor is first

asked to consent to the specific experiment planned and then to give consent to subsequent use for any other research.

The effect of a free and informed consent to the use of the donor's cells in the commercial sector, providing that the donor will not receive a share of any profit made, would be to negate any claim that the donor may otherwise have over the cells and any invention arising therefrom. This should be made an express term of the consent form. Nevertheless, it should be noted that in the UK, at least, such a consent may not be legally enforceable on the basis that the donor has not received any benefit in return, so the possibility of legal challenge remains.

Commercialisation of cell therapy products

Subject to the requirement that all applicable regulatory authorisations and approvals are obtained (see below) cell therapy products may be commercialised. There is no European legislation that specifically restricts the sale of therapeutic products derived from human tissue and indeed in recent years many European and national patents have been granted in relation to such inventions.

The Biotechnology Patent Directive makes clear that inventions consisting of or containing biological material are patentable and that patents for inventions containing biological material such as cell therapy products will be granted if the normal requirements of patentability are satisfied (ie the invention is new, non-obvious and has industrial application). However, under the European Patent Convention a patent will not be granted in relation to an invention the publication or exploitation of which would be contrary to 'ordre public or morality'.³ This exclusion is considered on a case by case basis and has already attracted considerable attention in relation to biotechnological inventions and transgenic animals, ie the Harvard Mouse case.⁴ However, for the majority of cell therapy products that may be envisaged it is difficult

to see how this exclusion could be applied against patentability.

The basic position under European law is that the first proprietor of any invention will be the inventor, although where an invention is made by an employee the entitlement to a European Patent will be determined by national law (and in many circumstances will reside with the employer).⁵ A potentially significant recent development in the area of proprietorship of inventions claimed from human tissue is that in the USA a patient advocacy group, which provided scientists with blood and tissue samples from patients, has joined with the researchers to file a joint patent application related to a disease-causing gene.⁶ This development is in line with the recommendations of the US National Bioethics Advisory Committee and the Human Genome Organisation that genetic researchers should share the benefits of their research with patients.

A further issue regarding the commercialisation of cell therapy products relates to the sourcing of the human tissue itself. In accordance with the Council of Europe Convention on Human Rights and Biomedicine, the NCB recommends that human tissue to be used by a commercial entity should be obtained only on a non-profit-making basis from sources subject to and governed by recognised codes of professional practice. In practice this means that a medical intermediary is required between donor and pharmaceutical company. The principle that human tissues should not be transferred for profit is reflected in what little UK legislation exists in this area. Under the Human Organ Transplants Act 1989 it is illegal to deal commercially in organs and similarly there are legislative restrictions imposed on trade in human gametes, embryos and restrictions on charges made by blood transfusion centres.⁷

Regulatory considerations

The answer to the question of whether cells can be treated as a medicinal product is yes, provided that the definition set out in

European medicines legislation⁸ is satisfied. There are no exclusions or additional requirements that specifically apply to either human or animal cells. Thus in the UK cell therapies may come under the control of the Medicines Act 1968 and therefore the authority of the Medicines Control Agency or more probably the European Agency for the Evaluation of Medicinal Products (EMEA). In the 'Points to Consider' paper on human somatic cell therapy released by the Committee for Proprietary Medicinal Products (CPMP) in December 1999 it is stated that for a human somatic cell therapy product to fall within the definition of a medicinal product it should *inter alia* 'be subject to an industrial manufacturing process carried out in dedicated facilities'.

Whereas for autologous approaches treatment is by definition bespoke to the patient undergoing treatment, allogeneic approaches may be applicable to whole populations. If allogeneic therapies are manufactured industrially they will be classified as medicinal products for the purpose of Directive 65/65. Thus for allogeneic cell therapy products to be commercialised a marketing authorisation will need to be sought. If the *ex vivo* manipulation of the selected cells involves certain biotechnological processes⁹ then a Community marketing authorisation must be sought through the EMEA rather than national authorities.

The CPMP paper referred to above sets out the principles to be taken into consideration when developing cell therapy products, the key objectives of which are to ensure that the product is consistent, of acceptable quality and free from contamination. Importantly, in relation to the sourcing of cells for therapeutic use this paper states that donors of allogeneic cells should be subjected to the same selection criteria as for blood and organ transplant donors. Also included in this paper is guidance related to, *inter alia*, the source and characterisation of materials used in the manufacturing process, cell culture and *in vitro* manipulation procedures and quality assurance. As indicated above, in the UK,

guidance on the use of human tissue and biological samples has recently been issued by the MRC.¹⁰

For autologous approaches such as dendritic cell-based cancer immunotherapy, in which dendritic cells are taken from the patient and activated *ex vivo* so as to trigger an immunogenic response when returned to the body, the requirement of industrial manufacture will not be satisfied. Accordingly, a marketing authorisation will not need to be obtained in relation to the cell therapy product itself (in this example the activated dendritic cells). Note, however, the possibility that the agents used to treat the cells *ex vivo* may themselves be regulated.

Other regulatory considerations

As stated above the range of therapeutic approaches covered by the definition of cell therapy is broad. Depending upon the nature of the cells that are to form the basis of the therapy and the manner in which they are to be manipulated it is possible that the therapy will fall into one or more of the following categories, necessitating the application of additional regulatory controls.

Xenogeneic cell therapy

The CPMP guidance note issued in December 1999 on the quality, preclinical and clinical aspects of gene transfer medicinal products advises that because of the greater risks associated with their use, primary xenogeneic cells should not be used in humans until an international agreement on xenotransplantation is reached. The United Kingdom Xenotransplantation Interim Regulatory Authority (UKXIRA) has been set up with the remit to handle all UK applications to undertake xenotransplantation. Note that the definition of xenotransplantation that is given in the UKXIRA guidance notes on making proposals to conduct xenotransplantation on human subjects is sufficiently broad to include any procedure that involves the transplant of live cells or tissues of non-

human origin (as well as the transplantation of whole organs). Therefore, in the UK for any human cell therapy approach using cells from a non-human animal source an application must be made to UKXIRA. The CPMP guidance paper sets out the additional regulatory considerations for xenotransplantation and describes the interaction between UKXIRA and other European and national agencies and regulatory systems.

Gene therapy

If the biological manipulation of cells *ex vivo* includes the genetic modification of human somatic cells then, in addition to the application of whichever of the aforementioned regulatory schemes are relevant, further national and European considerations will apply. For any gene therapy product to be commercialised in Europe it will require a marketing authorisation to be granted via the European licensing procedure rather than by the national competent authority. On a national level, in the UK the proposals will also be subject to the scientific and ethical scrutiny of the Gene Therapy Advisory Committee.

Stem cell-based approaches

In addition to using terminally differentiated cells, possible cell therapy approaches may include the use of stem cells capable of multiplying indefinitely and giving rise to many different cell types. It is thought that the transplantation of human stem cells may provide a renewable source of replacement cells and thereby offer a means of treating the large number of diseases that result from the disruption/ destruction of normal tissues (so-called 'regenerative medicine'). Although the medical potential is great, so too is the ethical debate surrounding research in this field, primarily because the origin of the pluripotent stem cells that would provide the source of any such therapy is human embryo or foetal tissue. The European Group on Ethics in Science and New

Technology has recently published a report on stem cell research.¹¹

The policy towards stem cell therapy in different European countries varies greatly. In Germany the extraction of stem cells from human embryos is forbidden, whereas in others stem cell research is partially permitted subject to regulatory approval. In the UK, the Human Fertilisation and Embryology Act 1990 (the HFE Act) governs research involving human embryos. In the absence of any statute governing the use of foetal tissue, guidance relating thereto has been laid down in a 1989 review of the Committee to Review the Guidance on the Research Use of Fetuses and Fetal Material. Schedule 2 of the HFE Act sets out the circumstances in which the Human Fertilisation and Embryology Authority (HFEA) may license human embryo research. Further to the publication of reports by the Human Genetics Advisory Commission, the HFEA, NCB and the Chief Medical Officer, the UK Parliament has recently voted in favour of amending Schedule 2 of the HFE Act to allow research involving human embryos to be permitted for the purpose of developing methods of therapy.

Stem cells derived from adults such as blood stem cells taken from bone marrow may also have clinical applications (ie haematopoietic stem cell therapy for the treatment of cancer, autoimmune and genetic disease). For obvious reasons therapies based on adult stem cells will not attract the same legal and ethical considerations as those derived from human embryos or foetal tissue.

Concluding remarks

Until more cell therapy products move from the laboratory to the market it remains to be seen whether, in the absence of a regulatory framework or agency dealing specifically with products derived from human tissue, the existing controls reflect the appropriate balance between safeguarding the rights of the patient or donor and the provision of an environment in which research into novel therapies is encouraged.

References

- 1 Moore v Regents of the University of California 793 P2d 479 (Cal 1990).
- 2 Recital 26 of Directive 98/44/EC on the legal protection of biotechnological inventions.
- 3 Art 53(a) of the Convention on the Grant of European Patents.
- 4 Harvard Oncomouse EPO T19/90 [1990] OJ EPO 476.
- 5 Art 60(1) of the Convention on the Grant of European Patents.
- 6 *Nature* Vol. 407, p. 821 (19 October 2000).
- 7 In respect of gametes and embryos see the Human Fertilisation and Embryology Act 1990; in respect of charges made by blood transfusion centres directions of the Secretary of State for Health pursuant to s. 25 of the National Health Service Act 1977 limit such charges to reasonable handling charges.
- 8 Article 1 of Directive 65/65/EEC.
- 9 Article 3 Regulation 2309/93/EEC (list of processes set out in Part A of the Annex).
- 10 MRC Ethics Series, 'Human Tissue and Biological Samples for Use in Research: Operational and Ethical Guidelines'.
- 11 The European Group on Ethics 'Adoption of an Opinion on Ethical Aspects of Human Stem Cell Research and Use', Paris, 14th November, 2000.

Copyright of Journal of Commercial Biotechnology is the property of Palgrave Macmillan Ltd. and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.