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Emerging Regulatory Issues for Human Stem Cell Medicine[1]

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Abstract

The regulation of stem cell research is an issue that has drawn much comment, criticism and even judicial arbitration in recent years. An emerging issue, addressed in this article, is how the fruits of that research—stem cell medicine—are likely to be regulated en route from lab to market. Taking account of the ethical, legal, social and safety issues raised by stem cell medicine and the goals of governance, the article explains the relevant regulatory instruments (e.g. the draft UK Stem Cell Bank Code, the EU Directive on Human Tissue, the EU Directives on medical products and devices, and the Human Tissue Act 2004) and critically examines the framework they provide.

Introduction

Human stem cell research is an energetic and vibrant field of science across the world – not least in the UK, US, Israel, China, Japan and Australia. Nevertheless, it is also something of a political, ethical, social and legal minefield, creating challenges for regulatory bodies, policy makers and scientists as they traverse their way through a tangled web of regulations and moral prosthelytizing. Profoundly difficult questions surround the morality of destroying embryos or using the remnants of aborted foetuses to improve the medical welfare of other human beings, and the morality of cloning human beings to improve the efficacy of the technique.[2] There has been extensive public debate about these topics,[3] which led to two pieces of legislation in the UK,[4] numerous legislative amendments in other countries,[5] and calls for an international resolution by the UN General Assembly.[6]

But whilst there has been much commentary on the regulatory framework that is needed to govern the derivation of stem cells, there has been negligible discussion of the regulation that will govern how the results of this research—stem cell medicine—will get from lab to market. This article investigates this question. It seeks to explain how stem cell medicine is likely to be regulated, and to identify areas where further attention is required. These issues are significant as the UK has recently established a special Stem Cell Bank which will be the first in the world to curate standardized human adult, foetal and embryo stem cell lines on a single site.

We have structured our discussion in the following way. First, we draw attention to the issues that ought to be addressed by the regulatory system given the foreseeable characteristics of stem cell medicine. Second, we consider the regulation that currently applies during product development and when seeking market approval.[7] In this section we focus on the regulatory system that is developing in the UK. On the question of stem cell research, the UK is widely regarded as having produced some of the most sophisticated regulatory solutions. Its cautiously liberal approach has also positioned it as a world-leader in the development of stem cell medicine.[8]

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Furthermore a series of new initiatives (e.g. the UK Stem Cell Bank, the East of England Stem Cell Network and the Cambridge Stem Cell Institute)[9] and new legal policy from the UK and European Parliaments mean a concerted effort to regulate regenerative medicine is already underway. Some £16.5 million of public funding[10] and £200 million of further funding from the private sector have been earmarked for research related to the development of stem cell medicine.[11] These features make it a particularly interesting and relevant case study for the future regulation of stem cell medicine. In the final section we reflect on some of the tensions and gaps that remain in the fledgling UK regulatory system.

Regulatory Objectives

1 Potential medical applications of stem cell research

Stem cell medicine can be described as strategies for successful regenerative medicine to treat diseases and abnormal conditions of the human body. The idea common to all stem cell medicines is that they exploit the pluripotency of stem cells, which are cells that replicate in an undifferentiated state for long periods of time whilst retaining the potential to develop into most tissues of the human body. If current research is successful, scientists will be able to trigger stem cells to develop into different kinds of tissue. Newly generated tissue could then be transplanted to reconstruct diseased or dead tissue or to correct tissue function. Clinical applications might also be developed to stimulate patients' own stem cells *in situ*, for example to prevent osteoporotic fractures.[12]

Research is presently being conducted on a wide range of clinical applications. Examples include research to develop blood and bone marrow cells for treatment of blood diseases; pancreatic islet cells for diabetes; neural cells for nervous system repair; tissues to repair blood vessels; and engineered tissues to enhance ordinary tissue function.[13] Most of this research is still at an early stage, though stem cell medicine derived from fetuses has been the subject of clinical trials in the US[14] and cell lines are in preclinical development for studies with Huntington's Disease and sufferers of stroke.[15] Researchers are keen to develop methods of deriving stem cell lines from human embryos cloned from an adult donor, using cell nuclear transfer. These stem cell lines are more likely to be immunologically compatible with the donor. Thus far, clinical-grade human embryonic stem cell lines have not been developed.[16] Since most countries restrict or prohibit the use of embryos in research, further experiments are being done to investigate the pluripotency of stem cells obtained from adults and fetuses.[17]

There are a number of scientific challenges.[18] Most significantly, stem cells must be retrieved without damaging them, coaxed to create a stable cell line, and stimulated to differentiate into the tissue of choice. Having created the tissue of choice, it must be separated from the culture and reagents, transplanted to the area of the body without destroying or destabilising it, and made to integrate with other cells and the vascular system in the area of the transplant. It is important that the transplanted tissue does not infect the patient with a disease from the original stem cell or tissues used to culture it. Establishing inter-cell communication is also significant so that the transplanted stem cell tissue does not prompt an untreatable immune reaction or grow in an unresponsive way to create a tumour.

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2 Emerging issues for the regulatory system

The purpose of regulation, broadly conceived, is to facilitate a social goal—in this case the commercialisation of stem cell medicine—whilst addressing social risk, market failure and concerns of equity and morality through rule-based direction of social and individual action.[19] On one view it involves three generic sub-objectives. First, regulation must reassure the end-users (patients and health care providers) that the product will reliably satisfy their needs without creating undue cost or moral concerns. In addition to stimulating rational demand, regulation also needs to stimulate supply. That is, it must reassure those who supply raw materials and labour that it is an enterprise in which it would be rational to participate. In the case of stem cell medicine, biotech companies provide the labour and some raw materials. However, critical raw material—stem cells and oocytes—must be provided by ordinary people (some from IVF programs, some self-donors, some with unusual cells,[20] and some people off the street). A different set of conditions will be needed to attract their participation. A third objective of regulating commercialisation (often overlooked by economic analysis) is the importance of encouraging responsible manufacturing processes. This is the glue that holds the regulatory system together, securing compliance with the spirit of legal policy rather than companies doing 'what they can get away with'.

(a) Reassuring End-users

(i) Safety and quality

End-users are primarily concerned that the innovative stem cell medicines have a high level of safety and quality, and will not be detrimental to their health. In this regard, regulation will need to ensure that cell lines used as the basis for stem cell medicines do not carry an infectious disease, viral disease or mycoplasma contamination.[21] These might be transferred to the recipient of the stem cell transplant. At a research level, mouse feeder cells are often used to help culture human stem cell lines. These may have negative or unknown side effects in humans. Moreover, transplanting animal cells into humans raises the legal and ethical issues surrounding xenotransplantation. It is difficult to separate the mouse feeder cells once they have been used as a culture, thus regulation is needed to ensure appropriate culture bases are used for clinical-grade stem cell lines, and that research-grade and clinical-grade cell lines are kept separate. Similar steps are necessary to ensure that the reagents used during the cultivation of stem cell medicines are safe for human use. Two further issues relevant to the safety of the stem cell medicines are tumourgenicity and antibiotic use. These must be quantified and within acceptable levels. Antibiotics are commonly used to identify cells of interest in a culture or to clean up contamination, however this can interfere with inter-cell membrane communication or lead to antibiotic resistance.[22]

Stem cell medicine may also challenge typical assumptions about the relative risks posed by autologous[23] and allogeneic cell transplants.[24] The former are routinely regarded as less risky because there is less chance of infection and immune reaction, and the process is usually carried out within one institution. A question raised by stem cell medicine is whether cell lines from cloned embryos are to be regarded as autologous (i.e. a transplant from/to the same person), and whether they are indeed less risky.

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To ensure stem cell medicines are of a satisfactory quality, regulation should insist that cell lines have stable characterizations in order that the safety risks are predictable. Relevant indicators include karyotyping and chromosomal analysis, gene expression, proliferative properties, bioassays and telomerase activities.[25] Current indications are that freezing and thawing cell lines can affect stem cells' characterisation, therefore conditions of storage should also be addressed.

(ii) Clinical efficacy or performance of claims

Promoting high levels of quality and safety in stem cell medicine is a highly technical issue, but there is much agreement that this is an important goal. A more controversial issue is whether stem cell therapies should be required to show that they have equivalent or better therapeutic potential than other therapies already on the market. Alternatively, we might be satisfied if regulation simply stipulates that stem cell medicines must do what the manufacturer claims they will do (e.g. replace diseased tissue with tissue of a certain characterization). These contrasting standards are sometimes referred to as, respectively, 'efficacy' and 'performance'. The distinction goes to the heart of the difference between the regulation of medical products and medical devices. Medical devices (e.g. pacemakers and syringes) are required to show that they perform in the way the manufacturer claims and in this sense are regulated in a similar fashion to non-medical engineered products.[26] The question of efficacy is left largely to market forces; if the device is less useful than other therapies, consumers will not purchase it. In contrast, medical products (stereotypically, pharmaceutical drugs) are required to fulfil the more demanding criteria of efficacy,[27] and to this end manufacturers will more often be required to conduct clinical trials. Whether the regulatory system opts for performance or efficacy will be a particularly pertinent issue for a stem cell medicine if it carries a risk of causing abnormalities (e.g. tumours) which other alternative therapies based on drugs or live-transplant do not.

(iii) Cost-efficiency

The regulatory framework for stem cell medicines will also need to attend to the issue of cost-efficiency if it is to satisfy end-users. The health system has a variety of mechanisms to investigate the cost-efficiency of medicines (e.g. the National Institute of Clinical Excellence), but the most fundamental approach is to stimulate a competitive market. The general theory is well known. Where there is competition between sellers, consumers get a better deal. The sellers vie with one another to produce a better product at a cheaper price. The important drivers are that there should be enough sellers to provide a range of products at alternative prices, and informed consumers who rationally choose between the products on offer.

Innovative technologies like stem cell medicine pose difficulties for a properly functioning market. There may be few companies with the necessary know-how, new players may be inhibited by the regulatory burden, and consumers may lack the ability to distinguish the better product from a worse one. Consumers are especially likely to be information-poor if manufacturers are not required to prove the efficacy of their product prior to market approval. Thus there is a complex tension between keeping regulatory burdens low, and having enough regulatory intervention to protect unsuspecting consumers.

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(iv) Embryo origins

It is also foreseeable that end-users will be concerned about the origins of a stem cell medicine, in particular whether it is based on an embryo stem cell line. Should regulation stipulate that users should be carefully briefed about the fact that the medicine was produced from embryos? The extensive debate in this country and many others about the use of embryos in research suggests that a considerable number of people are unhappy with the prospect of using embryos for medical ends and would want to be carefully briefed about the provenance of the therapy and have the opportunity to refuse to use therapies built from dead embryos. An analogy would be the respect that is given to the decisions of Jehovah's witnesses to refuse the transfusion of blood or primary blood products.[28] On the other hand, perhaps this approach would be unduly cautious. After all we are rarely, if ever, informed whether medicines have been tested on primates and given an opportunity to refuse or consent on the basis of that knowledge though some people find experiments that use higher-order primates morally troubling. Does this fail to respect us as morally autonomous beings? Perhaps we are satisfied to receive medicines based on the understanding that the regulatory system has considered the issues, and has set and monitored standards that are reasonable for a morally pluralist society.[29]

(v) Social impact

A further issue which end-users might be concerned to see addressed by regulation is the justice of stem cell medicine and its impact on social relations. It has been suggested that minority ethnic groups are unlikely to benefit equally from stem cell medicine if stem cell banks fail to include the less common tissue haplotypes.[30] Furthermore, stem cell medicine may be a cost-intensive technology that only the wealthy will be able to afford. In the longer term it is possible that stem cell medicine may significantly extend average life expectancies, which has attendant social complications. For instance, pension payments and inter-generational family disputes could increase dramatically.

(b) Reassuring Suppliers

(i) Property, intellectual property and minimal regulation

By and large, companies that provide labour and materials will be reassured by the regulatory system if it includes mechanisms that provide for clear and secure chains of title, allows them to recoup investment through intellectual property, and keeps regulatory burdens minimal.

(ii) 'Respect' for tissue, consent and minimum standards

Securing the trust of members of the public who are the source of the precursor tissue for the stem cell lines may be more challenging. Donors of tissues may consider their tissue to have a value different from the value that researchers and manufacturers attach to it. Donors may project some of the significance they place on their identity, reproductive capacities, physical integrity, and immortality onto the tissue that they are asked to donate for the purposes of stem cell medicine. That is, they may see the tissue as more than the sum of its biological parts.[31] Their attitudes are likely to be highly variable and policymakers will need to consider how they should regulate in the face of reasonable pluralism.

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(iii) Incentives for stem cell donations

There is more debate whether regulations should provide incentives to make people more willing to donate their tissues, for example by paying them, or giving them some other benefit in return. Some are concerned that this would lead to an unethical level of commodification that belittles human existence, or undermines altruism.[32] Others have argued that safety is compromised when financial incentives are offered since donors will have a reason to hide information about their medical histories.

(iv) Confidentiality and feedback

Medical testing is part of the process of donating tissue for stem cell medicine, in order that the safety and quality of the tissue can be assessed. This involves screening for certain infectious diseases and genetic traits, and blood typing. This produces sensitive information that many donors may or may not wish to know, nor wish others to know. Therefore, the regulatory framework will need to protect the confidentiality of donors and set standards relating to feedback of information.[33]

(c) Encouraging Responsible Manufacturing Practice

Mechanisms to ensure responsible manufacturing practice are difficult to define precisely or exhaustively. In large part, the objective is to keep manufacturers sufficiently 'on their toes' so that they observe the regulatory policy, and sufficiently 'sweet' so that they cooperate with regulators without the need for costly prosecutions. In practical terms, this means stimulating a healthy level of competition, keeping regulatory burdens to a minimum, providing incentives in the form of intellectual property or free regulatory advice, and enforcing the regulatory framework sensibly (i.e. without extreme formalism or undue regulatory 'slack').[34] A pyramid system building up from self-regulation, registration and licensing, civil liability and finishing with a few criminal penalties for the worst breaches is argued by some to work well.[35]

Regulation: From Lab to Market

We turn now to consider the regulatory system emerging in the UK, as influenced by European and national legislation and policy.

1 Product Development

(a) EU Tissue Directive 2004

European Member States recently (March 2004) agreed, after protracted debate within the European legislative machinery, a common regulatory framework to ensure the safety of cells and tissues that are transplanted into, or onto, the human body.[36] One reason for the delay was that the European Parliament tried, indirectly, to prohibit therapeutic cloning and embryo stem cell research under this instrument.[37] Those provisions were eventually discarded.[38] The directive—titled "on setting standards of quality and safety of the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells"—will apply, amongst other things, to stem cell medicines but not the preceding *in vitro* research. Member States, and therefore the UK, are obliged to implement the directive by April 2006.

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The Articles most relevant to ensuring clinical-grade tissue development are those on testing, processing, donation, and procurement. The precise technical requirements are merely outlined in Article 28, and are yet to be decided by the Commission, pursuant to the procedures in Article 29. Draft technical requirements for donation, procurement and testing have been published for consultation.[39] A second set of technical requirements on processing, preservation, storage and distribution is expected in the near future. It is anticipated these will cover requirements for quality systems and coding.[40]

In broad terms, donated and processed tissue must be tested for infection (e.g. HIV, hepatitis and syphilis) and characterized. Living donors of allogeneic tissue are required to undergo a prior medical examination and interview. The Directive also stipulates that donors should not be paid, for reasons of safety rather than ethics.[41] Matters of ethics were regarded as issues that the European Union was not competent to legislate upon.[42] Issues of data protection and consent were covered to a limited extent. The Directive states that the European Directive on the processing of personal data must be observed[43] (this is already binding on Member States). It also states that the laws on consent in each Member State must be observed when tissue is procured from donors.[44]

Safety and quality are addressed in a set of rules on product recall, preservation, storage, labeling, packaging and adverse incident reporting.[45] No specific provision is made for compensation where a patient is harmed by a tissue therapy, although a claim might be made through product liability laws, including the law of negligence and consumer protection legislation.[46] It is doubtful however that these laws will assist an end-user who suffers emotional distress on finding out that they were treated with a product derived from embryos, but does not develop a recognized psychiatric condition.[47]

To ensure that the rules are adhered to and that the premises are suitable for the development of clinical-grade tissue therapies, each Member State is responsible for seeing that establishments that handle relevant tissue are licensed and follow a quality assurance system. Strict rules on the traceability of product development will also apply to achieve rigorous accountability.

The Directive does not apply to autologous grafts *within the same surgical procedure*.[48] The latter phrase is significant. For instance, if autologous tissue is banked it *is* covered by the Directive.[49] This suggests embryo stem cell medicine is likely to be covered by the Directive, whether or not it is considered an autologous procedure, since the activity required to clone a blastocyst is likely to require more than a single surgical procedure.

(b) Human Tissue Act 2004

Until the directive is implemented the standards noted above have no legal equivalent in the UK, aside from laws that protect donors of tissue. These laws, most notably the Data Protection Act 1998 and (until recently) the Human Tissue Act 1961, have been the source of much debate. Parliament has recently repealed the latter after the furore following the non-consensual retention of organs following post-mortems at hospitals in Bristol, Liverpool and elsewhere.[50] It has enacted in its place a much more extensive piece of legislation, the Human Tissue Act 2004 (HTA), which is expected to commence in April 2006. The fundamental principle underpinning this Act is that

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individuals should have the opportunity to choose whether or not tissue lawfully taken from their bodies is subsequently retained or used for medical research. Accordingly the Act makes it a criminal offence to use human tissue (excluding gametes and embryos) in research without the prior consent of the individuals. The Act also regulates tissue disposal, trafficking of controlled materials, and DNA analysis of tissue. However, somewhat surprisingly, the government's Explanatory Memorandum indicates that none of the various protections the Act introduces[51] apply to human stem cell lines by virtue of the clause which excludes tissue 'created outside the human body'.[52] This policy decision is perplexing in its ethical dimensions—surely donors of tissue for stem cell medicine are entitled to the same protection as donors of tissue for orthodox tissue transplants? The policy enacted goes well beyond the policies contemplated in the government's discussion paper preceding the legislation. These included the idea that *anonymised* cell lines might be used or stored without consent, or that donors might be asked to give up property and other economic rights in cell lines (but not all power to restrict the use of cell lines derived from them).[53]

(c) Codes and Guidance

(i) Tissue-related

To date, the safety of human tissue product development has been regulated by codes rather than law. The three principal codes in this regard were prepared by the Medical Devices Agency (MDA),[54] and the Department of Health.[55] The MDA's code includes rules on characterizing quality, batch control, infection controls, risk minimization, certificates of raw material analysis, scaffolds, donor screening, cell culture preparation, and full passage data. Other rules recommend procedures to prevent contamination, tampering and deterioration, and labels that advise on handling and hazards. The Department of Health's guidance is equally technical and detailed. The Codes were published in 2000 to 2002 and will need to be brought up-to-date for the purposes of stem cell medicine, particularly if stem cells are combined with nanotechnology and genetic technology to develop 'intelligent' regenerative structures.[56] In conjunction with these codes, the Medicines and Healthcare products Agency (MHRA) has encouraged therapeutic tissue banks to apply for voluntary accreditation.[57]

(ii) UK Stem Cell Bank

As noted, the UK has taken the bold new step of setting up a dedicated national Stem Cell Bank. It is the first in the world to curate standardised human adult, foetal and embryonic stem cell lines on a single site.[58] The Bank will house clinical-grade stem cell lines and establish approved facilities for processing them. It issued a Draft Code which broadly outlines the criteria to be observed when deriving and using human stem cell lines.[59] A companion code specifies the conditions for accessing stem cell lines in the bank.[60]

The Draft Code is ostensibly similar to the standards set out in the European Tissue Directive and codes on tissue therapies mentioned above. It also covers cryopreservation, import/export, and transportation of stem cell lines.[61] The International Stem Cell Forum has set up a working group to design indicators specially suited to characterizing embryo stem cell lines.[62] Sections 5 and 6 of the Draft Code set rules covering donor selection, screening, information and consent,

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and prohibiting payment. The central idea is that donors are asked to gift their stem cells, relinquishing all future control, after comprehensive information is provided to them about the implications of doing so. A further pre-requisite is that they consent to provide a medical history and allow genetic testing. Their data will be kept confidential, but traceable. Embryo donors may select one of three conditions for feedback on disease that might be discovered in the future (where it concerns their sample): no feedback; feedback where there is, or is potentially, a therapy; or feedback in any circumstance.[63] This contrasts with UK blood donation guidelines that, in an effort to minimise the numbers of donations that compromise public health, state that putative donors should be told that information about significant abnormal results *will* be fed back to them; blood donors are not permitted to stipulate that no feedback should occur.[64] To boost accountability to the standards, and avoid conflicts of interest, the Bank has decided it will not conduct discovery research itself.[65]

Not all stem cell developers will be bound by the Draft Code, only those who sign a contract to use stem cell lines from the bank. However, the principles are likely to reflect closely the MHRA requirements for market approval (see below), and the Medical Research Council (MRC) will require those who receive its funding to observe the Bank's rules.[66] The Draft Code will apply more strictly to embryo stem cell lines because the Human Fertilisation and Embryology Authority (HFEA) has decided that it will make compliance with the Draft Code a condition of all its licenses for embryo stem cell research, and will require a sample of all embryo stem cell lines to be deposited with the Bank.[67] One justification for the differential treatment of embryonic and somatic stem cell lines is that mandatory banking will minimize the numbers of embryos that are used, which some say is a mark of 'respect'.

The level of oversight seems to be tight. Detailed 'route maps' show the system for accessing a stem cell line.[68] The Bank has also indicated that, in relation to embryonic stem cell lines, its approval must be obtained before involving new collaborators from a different institution or new projects on the same cell line, and it should be notified of new and departing staff.[69] Nevertheless, the degree of real intervention remains unclear; the Bank may do little to enforce these requirements.

(d) Property and Intellectual Property Rights

The Draft Code from the UK Stem Cell Bank envisages that stem cell lines will remain the property of depositors, and that depositors will negotiate Materials Use Licenses with each would-be accessor to protect their proprietary interests.[70] Intellectual property rights can be asserted in these licenses. Some 'reach-through claims' could be expected (patent claims or license terms asserting a right to a share of revenue generated from downstream products, methods and protocols), but these are unlikely to be as controversial as reach-through claims stemming from gene patents, which cannot be invented around.

The UK Patent Office is willing to grant patents to applicants claiming pluripotent stem cell lines retrieved from human embryos,[71] as well as somatic stem cell lines (provided the standards of novelty, inventiveness, industrial applicability, sufficient disclosure are demonstrated). However, the European Patent Office's Opposition Division has interpreted the wording of the morality clauses in the EU Directive on the legal protection of biotechnological inventions differently.[72] On its view, the same policy would not be lawful under the European Patent Convention.[73] Unless the ruling is reversed on appeal, the implication is that inventors will have to

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apply to national patent offices in each of the European countries where they hope to patent a stem cell line isolated from human embryos.[74] Until the interpretation of the EU Directive is clarified, individual Patent Offices are likely to adopt differing views about the patentability of stem cell lines isolated from embryos.

(e) Confidentiality and Feedback

Given that the EU Tissue Directive and the various codes stipulate that donors' samples and records should be traceable (meaning their identity is encrypted but accessible), it is likely that the data will fall within the definitions of personal data (under the Data Protection Act 1998) and confidential information (at common law). This would be the case where the data controller (a term defined under the Data Protection Act) holds the data encryption key, rather than an independent third party. In this case, users of the information would ordinarily need the consent of the person or persons who are identifiable from the information in the user's possession. The Data Protection Act 1998 is clear that this should be explicit consent, but neither it nor the common law clarify the specific information that must be given to ensure the consent is valid. The Annex to the EU Tissue Directive provides some guidance but this only applies in so far as it is consistent with Member States' national legislation and thus may not be binding.[75] Some scholars have also questioned whether genetic screening necessitates a special attitude towards consent, for example that consent should be sought from close family members prior to use or disclosure.

2 Market Approval

(a) Current Standards for Authorisation

Before a new medical product can be released, it must be approved for market release by the European Commission, or the UK Licensing Authority (Health Ministers) as advised by the MHRA. Strictly speaking, a new medical device does not require prior authorisation in the same way. A device is either 'self-certified' (the manufacturer declares the device meets the requirements under the relevant European medical device directive) or it passes a conformity assessment process with a 'Notified Body' (an independent (commercial) body which has been approved by the MHRA as suitable for carrying out such assessments). The crucial question is whether stem cell medicine is required to meet the criteria of the Medicinal Products Directive[76] or the less demanding Medical Devices Directive.[77] The answer is less than obvious if one looks to the central definitions of medicinal products or devices (see boxed figures 1 and 2).

Figure 1 Definition of Medicinal Product[78]

(a) any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
(b) any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis

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Figure 2 Definition of Medical Devices[79]

any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:
- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means

Against these definitions stem cell medicines appear to be a borderline product. The distinction can be important as it affects the stringency of oversight. Furthermore, as mentioned, medicinal products are required to show clinical efficacy as well as safety and quality, and to this end a manufacturer must conduct clinical trials as necessary. With medical devices, on the other hand, manufacturers are (by and large) required to show only that a device performs as claimed and that its benefits outweigh the risks it poses to users. In practical terms, an evaluation of existing literature will frequently suffice and clinical trials are less commonly required.[80]

On closer inspection it appears that, at the present time, stem cell medicines will be treated as medicinal products since the Medical Devices Directive specifically excludes cells and tissues of human origin.[81] This categorisation is not an absolute rule,[82] nor a particularly apt one even after the Medicinal Products Directive was amended to include advanced technologies.[83] Thus the former UK Medicines Control Agency (MCA) and the former MDA (now amalgamated in the new MHRA) both took steps to set some indicative standards.[84] There are still some ambiguities and gaps. Tellingly, both the MDA and the UK Stem Cell Bank recommend that 'regulatory guidance should be obtained from the medicinal authorities on cell lines/tissues arising from stem cell technologies'.[85]

Interestingly the codes have narrowed the distance between the concepts of efficacy and performance. For instance the MDA code requests evidence that shows more than performance and states that 'where possible' developers should demonstrate 'a correlation with clinical effectiveness', and compare the product with the best clinical alternative for treatment through randomised clinical trials.[86]

(b) Proposed EU Regulation for Human Tissue Engineered Products

The vagueness within the current regulatory framework has led to considerable dissatisfaction:

> "At present, the lack of a comprehensive, clear and uniform regulatory framework creates legal uncertainties and leads to a fragmentation of the tissue engineering market: similar products are regulated differently in the various Member States, different safety requirements may apply and patients

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> can be denied access to products which are readily available in other countries."87

Some also consider the current rules deficient because the standards they set for autologous cell therapies are too lax in some circumstances. In response to these concerns, the European Commission has proposed a Regulation for human tissue engineered products, which it consulted on in 2002-2004.[88] It proposes a single regime for human tissue engineered products, clear demarcation from medicinal products and devices, and safety standards for autologous and allogeneic tissues that reflect levels of risk and minimize regulatory burdens for single application tissues. It is expected that a draft Regulation along these lines will be circulated for public consultation in 2005.[89]

(c) Clinical Trials Regulations 2004

As and when stem cell medicine trials begin, the new UK Clinical Trials Regulations (CTR), which came into force on 1 May 2004, will apply.[90] This instrument provides a statutory footing for good clinical practice, good manufacturing practice, research ethics committee review, informed consent of trial participants, and legal liability for injuries.[91] If a new Regulation distinguishes tissue-engineered products from medicinal products, the CTR may need amendment to cover these products.

The Adequacy of Current Regulation

1 Reassuring End-users

Many steps have been taken to ensure that the UK regulatory system promotes safe and high quality stem cell medicines, and addresses tumourgenicity, stability, adventitious agents, antibiotics use, freezing and the like. These apply to tissue generally and stem cell medicines specifically. Additional work is underway to improve the expertise and consistency of oversight.[92] It seems the authorities are also taking a holistic approach to the regulation of safety and quality, as evidenced by the introduction of regulatory mechanisms that apply long before a product seeks market approval and strict traceability.[93]

But whilst the issues of safety and quality have been thoroughly and openly addressed, other factors relevant to reassuring end-users have been neglected in comparison. One oversight has been the failure to discuss how the system will ensure compliance. To date, regulation has largely been soft rather than strict until the point at which MHRA approval is sought. This may continue even after the EU Tissue Directive and the Draft Code from the UK Stem Cell Bank are implemented.[94] The decision is relevant to the cost-efficiency of the system. The approach needs to improve the imperfections of the market, acting on behalf of information-poor consumers, without creating a weightier set of problems by adding regulatory red tape that hinders competition. The fact that there is only one UK Stem Cell Bank could create an anti-competitive bottleneck if it is not managed carefully. In effect, it has a monopoly on the banking of embryo stem cell lines and has a heavy responsibility to oversee those resources in an efficient manner.

There is also a question whether the system does enough to ensure manufacturers are sufficiently accountable to *patients* injured by stem cell medicines, as opposed to the official regulators. The myriad of codes does little to address this

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point. The Draft Code merely tries to exonerate the Stem Cell Bank of any responsibility, stating that stem cells are provided without any warrant of their merchantability or fitness for purpose.[95] Whilst consumer protection law might assist to some degree, a discussion about its adequacy is noticeably absent in the governance documents. These also fail to discuss the interest an end-user has in knowing that a stem cell medicine they are offered to them is derived from destructive research with embryos. The documents fail to discuss this even in the context of labeling.[96] Similarly, policymakers seem not to have considered the wider social issues relating to equity of access and resource allocation which academics have noted as being important. Further discussion is needed to establish how these matters might best be addressed.

There is also a lack of clarity on the issue of efficacy versus performance of manufacturers' claims. It is difficult to discern which standards manufacturers are required to meet, and it is odd that this issue was not discussed in the consultation documents on the proposed Human Tissue Engineered Products Regulation. There are empirical and normative issues at stake–for instance, how should one measure the efficacy of stem cell medicines; should efficacy be a *pre-requisite* for market-release of such an innovative therapy; and should the data on embryo-derived stem cell medicines be made available to the HFEA which must consider the necessity and desirability of license applications for the use embryos in research?

2 Reassuring Suppliers

In terms of its ability to reassure suppliers, the current UK regulatory system has some significant shortcomings, but is not acutely flawed. Policymakers have foreseen the issues of property and intellectual property in stem cell medicines. The Draft Code which has made provision for Materials Use Licenses, the UK Patent Office and the HTA have all taken steps to recognise explicitly developers' property and intellectual property in stem cell lines. Nevertheless, a good deal of uncertainty persists. Case law on the amount of skill and labour that is necessary to ground a property claim in human tissue is unclear (the HTA has not clarified it); and intellectual property rights available under the European Patent Convention (an administratively easier route than applying through national offices) are in a state of flux.

The developers of stem cell medicines must contend with a daunting regulatory burden, especially considering the majority of companies in this business are small- to medium-size enterprises. The applicable regulations are numerous, complex and growing, and their full impact will not be known until methods of compliance and enforcement become clearer. It may turn out that the variety of legislation is defensible as a tailored 'pyramid'. The UK Stem Cell Bank, together with its red tape, may also turn out to be a boon to smaller businesses if it lowers transactions costs and helps them develop compliance tools. We suggest this issue be monitored, and that State-sponsored initiatives to explain the regulatory system be introduced.[97]

Deeper problems surround the sufficiency of the regulatory system for protecting the interests of individual tissue donors. It is remarkable that donors of stem cells have the least legal protection of all tissue donors. Despite recent policy reform in the form of the HTA and the EU Tissue Directive, UK legislation does not stipulate that developers must respect the limits of stem cell donors' consent. For instance, if an individual were to state "I consent to you using my tissue to create a

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stem cell line, but in years to come I do not wish pharmaceutical companies to have access to the cell line because of the way my family was treated in a clinical trial", no liability would follow if the developer did in fact contravene the latter condition. Once a stem cell line is created, it falls outside the remit of the HTA. In contrast, conditions of consent will be binding under the HTA when other kinds of tissue are used by developers and even where pathologists inspect resected tissue for the purposes of basic research. If the developer thinks the putative donor's restrictions are unworkable, he or she is expected to avoid criminal liability by declining the tissue donation. Developers of stem cell medicines will perhaps decide to work in this way as well. But in the event they do not, donors whose tissue is used as a pre-cursor of a cell-line are left to rely on common law and the less formal powers of the UK Stem Cell Bank and the MRC. The latter two cannot force compliance from companies who develop somatic stem cell medicines with private funding and without using cell lines deposited in the Bank. Research ethics committees offer another line of protection, but at present it is doubtful whether they monitor compliance with consent requirements once they have approved a proposal. We leave open the question whether strict requirements for consent are the appropriate way to protect individuals' interests in their tissues, but would argue that the exclusion of stem cells from the HTA framework deserved considerably more debate. The question for present purposes is whether a legislative requirement should be added when the government implements the EU Tissue Directive, or whether individuals' interests in their tissues can be properly observed through another regulatory mechanism.

In terms of paying individual donors for their tissue donations, government resistance has shown signs of thawing[98] but payments will not be allowed at either the UK or EU level where cells or tissues are used for transplantation. It will take a groundswell to alter this position now that it has been backed by legislation. Therefore, it might be pertinent to consider other methods of motivating donors to donate.

The regulatory system does provide some reassurance in terms of donor confidentiality and rights to feedback. But its application is unfortunately vague and complex for the development of stem cell medicines, which involves incomplete anonymisation and compilations of genetic information.

3 Encouraging Responsible Manufacturing Practice

A number of positive steps have been taken to encourage responsible manufacturing practice in the UK. The UK Stem Cell Bank has signalled that it intends to work in partnership with industry to help them innovate efficiently, as well as to understand their ethical responsibilities. Furthermore, policymakers are aware of the importance of a level playing field[99] and have given industry opportunities to contribute to consultations. Together with the extensive range of standards, these steps go a long way towards maintaining an effective climate of respect and cooperation with the regulators. Maintaining this balance in practice will not be easy. Several critical issues are yet to be navigated. The authorities need to decide how they will check whether guidelines are being observed, and what they will do when they first notice that a licensee is not observing the legislation or guidelines. If the line they take is too tough, companies may cease cooperating and look more aggressively for ways to avoid the regulatory pinch or abandon the technology. If too soft, industry may come to regard ethical responsibilities as optional. Another issue yet to be tackled with

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vigour is biomedical companies' ethical duty to share the profits that derive in part from altruistic donations by members of the public.

4 A Final Word on Stem Cell Exceptionalism

Academic debate on the regulation of stem cell medicine is remarkable for its scarcity, but does this mean the issues are extraordinary and in urgent need of legislators' attention? We think this conclusion would be too strong. The scientific progress associated with stem cell medicine does not enter a regulatory vacuum. The law is designed to adapt to changing social circumstance. Nevertheless, there are several emerging regulatory issues that deserve closer scrutiny. None of these issues are unique to the regulation of stem cell medicine but quite a number are uncommonly encountered; for instance the s 54(7) exemption in the HTA, the new Stem Cell Bank with regulatory powers but no statutory standing, the interpretation of morality-based prohibitions on patenting in intellectual property law; unusual market dynamics and unfamiliar scientific risks (in particular in relation to autologous tissue transplants). In addition, we observed a number of issues that regularly arise in other fields of biolaw but which are no less important for being seen before. In summary, scant attention to methods of enforcement and compliance, vagueness about the criteria for market approval owing to the uncertainty surrounding the borderline between a product and a device, data protection law, information required for valid consent, the exceptions to the 'no property in the body or body parts' rule, and ethical debate about the extent to which the law should recognise donors' proprietary, economic and other rights in cell lines derived from their tissue. Hopefully these issues will be the focus of further inquiry by scholars from a wide variety of backgrounds without giving rise to a new kind of regulatory exceptionalism.

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[1] An earlier version of this paper was given at the Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK, organized by the CGKP and Cambridge Centre for Stem Cell Biology and Medicine. A related paper by KL was presented at the Human Tissue Workshop, 20-21 January 2004, organized jointly by the CGKP and the King's College Bioethics Research Centre. Whilst remaining responsible for all errors and opinions, the authors would like to thank the participants at both these meetings for their insight on the science and policy issues, Alison Hall (CGKP) for her particularly thorough assistance on matters pertaining to the Human Tissue Bill, Dr Ron Zimmern (CGKP) and Sandra King (Mills & Reeve) for helpful suggestions on an earlier draft.

[2] On the ethical issues raised by stem cell research: S. Holm. Going to the Roots of the Stem Cell Controversy. Bioethics 2002; 16(6): 493.

[3] On the legal policy debates: R. Brownsword. Stem Cells, Superman and the Report of the Select Committee. Modern Law Review 2002; 65(4):568-87.

[4] To facilitate the research: Human Fertilisation and Embryology (Research Purposes) Regulations 2001. To limit the application of the research (i.e. to prevent reproductive cloning and baby-organ farming): Human Reproductive Cloning Act 2002.

[5] L. Knowles. A Regulatory Patchwork – Human ES Cell Research Oversight. Nature Biotechnology 2004; 22(2):157-163.

[6] See http://www.un.org/law/cloning/ (accessed 14/02/05).

[7] We focus on the laws that apply in the UK. For international approaches, see M. Lloyd-Evans. Regulating Tissue Engineering. Materials Today 2004; May: 48-54, 50-3.

[8] E.g. speech by Lord Warner, Parliamentary Under-Secretary of State in the Lords, 19 May 2004: Launch of UK Stem Cell Bank.
http://www.dh.gov.uk/NewsHome/Speeches/SpeechesList/SpeechesArticle/fs/en?CONTENT_ID=4084091&chk=YtRkby (accessed 30/07/04); Bioscience 2015: Improving National Health, Increasing National Wealth report http://www.bioindustry.org/bigtreport/index.html (accessed 30/07/04); House of Lords Select Committee Report on Stem Cell Research 2002, 33.

[9] Research Councils UK. 27 May 2004. Research Councils Announce £16.5m investment in Stem Cell Research. http://www.rcuk.ac.uk/press/20040527stemcellres.asp (accessed 30/07/04); M. Lysaght and A. Hazlehurst. Private Sector Development of Stem Cell Technology and Therapeutic Cloning. Tissue Engineering 2003; 9(3):555-559.
[10] Research Councils UK. 27 May 2004. Research Councils Announce £16.5m investment in Stem Cell Research. http://www.rcuk.ac.uk/press/20040527stemcellres.asp (accessed 30/07/04).
[11] M. Lysaght and A. Hazlehurst. Private Sector Development of Stem Cell Technology and Therapeutic Cloning. Tissue Engineering 2003; 9(3):555-559.
[12] P. Bianco et al. Stem cells in Tissue Engineering. Nature 2001;414:118, 121; D.A. Steindler et al. Stem Cells and Neuropoiesis in the Adult Brain. Lancet 2002; 359:1047-1054 as cited in European Commission. 2003. Report on Human Embryonic Stem Cell Research. ftp://ftp.cordis.lu/pub/rtd2002/docs/sec441final.pdf (accessed 27/07/04). Some researchers are also pursuing stem cell medicines with add-on technologies involving genetic modification and nanotechnology: G. McAllister. Stem Cells and the Pharmaceutical Industry. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[13] V. Silani et al. Stem-Cell Therapy for Amyotrophic Lateral Sclerosis. Lancet 2004; 364:200-202, M.A. Hussain et al. Stem-Cell Therapy for Diabetes Mellitus. Lancet 2004; 364:203-205; The European Association for Bioindustries. 2003. Human Cell and Tissue Based Products. http://www.europabio.org/documents/CandT.pdf (accessed 07/02/05).
[14] R.N. Rosenberg. Positive Potential of Fetal Nigral Implants for Parkinson Disease. Archives of Neurology 2004; 61:837-838.
[15] J. Sinden. Stem Cells and the Biotech Sector. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[16] On the most recent success: W.S. Hwang et al. Evidence of a Pluripotent Human Embryonic Stem Cell Line Derives from a Cloned Blastocyst. Science 2004; 303:1669-1674.
[17] C.M. Verfaillie. Adult Stem Cells: Assessing the Case for Pluripotency. Trends in Cell Biology 2002;12(11):502-508. The UK allows researchers to use embryos in research aimed at developing stem cell medicines but only where they obtain a licence from the Human Fertilisation and Embryology Authority (HFEA). The law states that the HFEA may only grant a licence where the proposed use of embryos in research is necessary or desirable. The HFEA announced in August 2004 that it had granted its first research licence to create embryos using cell nuclear transfer (cloning) to the International Centre for Life in Newcastle http://www.hfea.gov.uk/PressOffice/Archive/1092233888 (accessed 17/09/04). A special interest group has commenced proceedings for judicial review arguing that the licence was improperly granted, in part because the HFEA had not established that the research was 'necessary or desirable'. The High Court has agreed to grant a hearing on the matter. http://www.lawcf.org/dox/pdf_104.pdf (accessed 07/02/05).
[18] National Institutes of Health. 2001. Stem Cells: Scientific Progress and Future Research Directions. http://stemcells.nih.gov/info/scireport/ (accessed 27/07/04); European Science Foundation Policy Briefing. 2002. Human Stem Cell Research: Scientific Uncertainties and Ethical Dilemmas. http://www.esf.org/publication/142/ESPB18.pdf (accessed 27/07/04); European Commission. 2003, op cit note 12.
[19] Adapted from B Morgan and K Yeung. 2002. Regulation: Course Materials. University of Oxford.
[20] For example, there is some interest in establishing stem cell lines from schizophrenic patients (at present in order to identify new drugs): G. McAllister. Stem Cells and the Pharmaceutical Industry. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[21] President's Council on Bioethics. 2004. Monitoring Stem Cell Research. http://www.bioethics.gov (accessed 26/07/04).
[22] Draft Code [7.11].
[23] Autologous transplants are transplants where cells or tissue are obtained from one person and returned to the same person.
[24] Allogeneic transplants are transplants where cells or tissue are obtained from human sources other than the patient.
[25] J. Sinden. Stem Cells and the Biotech Sector. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[26] The essential requirements are found in Annex 1 of each of the three applicable medical device directives: 90/385/EEC (active implantable medical devices), 93/42/EEC (medical devices) and 98/79/EC (in vitro diagnostic medical devices). For example, Annex 1.3 of 93/42/EEC states that 'The

devices must achieve the performances intended by the manufacturer…'. On the performance standard, see: G Higson. 2002. Medical Device Safety: The Regulation of Medical Devices for Public Health and Safety. Institute of Physics Publishing, 163-4.

[27] Medicines Act 1968, s.19.1(b).

[28] See e.g. *HE v A Hospital NHS Trust* [2003] Family Law 733.

[29] One of us has elsewhere considered the theoretical foundation for the legitimacy and fairness of biolaw: K. Liddell. 2003. Biolaw and Deliberative Democracy. DPhil thesis; University of Oxford.

[30] H. Bok et al. Justice, Ethnicity, and Stem-Cell Banks. Lancet 2004; 364:118-121.

[31] C.A. McMahon et al. Embryo Donation for Medical Research: Attitudes and Concerns of Potential Donors. Human Reproduction (2003); 18(4):871-877, 874-875; M.J. Meyer et al. Respecting What We Destroy: Reflections on Human Embryo Research. Hastings Center Report 2001; 16, 18, 21.

[32] For critical discussion of the main arguments: S. Wilkinson. 2003. Bodies for Sale: Ethics and Exploitation in the Human Body Trade. London. Routledge; K. Baum. Golden Eggs: Towards the Rational Regulation of Oocyte Donation. Brigham Young University Law Review 2001; 107:134, 137, 158-9 (in relation to market incentives for oocyte donation); D.B. Resnik. The Commodification of Human Reproductive Materials. Journal of Medical Ethics 1998; 24:388, 393.

[33] See generally G. Laurie. 2002. Genetic Privacy. Cambridge. Cambridge University Press; J.V. McHale. Regulating Genetic Databases: Some Legal and Ethical Issues. Medical Law Review 2004; 12: 70-96.

[34] K. Yeung. 2004. Securing Compliance: A Principled Approach. Oxford. Hart. 158-162.

[35] I. Ayres and J Braithwaite. 1992. Responsive Regulation—Transcending the Deregulation Debate. New York. Oxford University Press.

[36] Directive 2004/23/EC.

[37] European Parliament (Committee on the Environment, Public Health and Consumer Policy). 25 March 2003. Report on the proposal for a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, storage, and distribution of human tissues and cells—A5-0103/2003. The Committee put forward an amended legislative proposal that prohibited the creation of human embryos solely for research purposes, research on embryos to supply stem cells, and research to supply stem cells through cell nuclear transfer (Art 4(2b)). Recital 13 added a further bolt to the door, stating that Member States 'must fully respect' the Council of Europe's Convention on Human Rights and Biomedicine, which in turn prohibits the creation of human embryos for research purposes (art 18(2)).

[38] European Parliament Daily Notebook for 16-12-2003: Human Tissues and Cells. http://www2.europarl.eu.int/omk/sipade2?PUBREF=-//EP//TEXT+PRESS+DN-20031216-1+0+DOC+XML+V0//EN&LEVEL=3&NAV=S#SECTION3 (accessed 07/02/05).

[39] European Commission. 3 August 2004. Draft Technical requirements for the donation, procurement and testing of human tissues and cells. http://europa.eu.int/comm/health/ph_threats/human_substance/oc_tech_cell/oc_tech_cell_en.htm (accessed 27/09/04). These reflect the indicative technical standards set out in appendices annexed to the draft directive (2002/C 227 E/28): See OJ 2002;C 227 E: 505-521.

[40] See http://www.hfea.gov.uk/HFEAPublications/EUTissuesAndCellsDirectiveNewsletter/EU%20%20Directive%20November%20merged.pdf (accessed 12/02/05).

[41] Recital 19.

[42] The Commission stated that it gave the ethical provisions suggested by the European Parliament 'careful consideration and can accept those related to the anonymity of donors and/or non-profit procurement …Other proposed ethical provisions cannot be accepted, however, as they fall outside the scope of Article 152, that provides for public health protection and not the implementation of ethical objectives as such.': European Commission. 28 May 2003. Amended proposal for the EU Tissue Directive (COM(2003) 340 final), para. C(1).

[43] Article 14; Recital 24 referring to Directive 95/46/EC.

[44] Article 13. In the UK, relevant laws include the Data Protection Act 1998, the common law of confidentiality, the HTA 2004 (for tissue obtained from deceased persons), the Human Fertilisation and Embryology Act 1990 (for donations of embryos and gametes), and the law on battery and negligence (for tissue obtained from living persons).

[45] Articles 11, 21 and 22.

[46] The EU directive simply stipulates that member states shall set 'dissuasive' penalties (Art 27), which suggests that criminal liability or revocation of licence will follow a breach.
[47] A successful action under the Consumer Protection Act 1987 is also made difficult by the controversial 'development risks defence', under which it is a defence for the producer to show that, at the relevant time, the state of scientific and technical knowledge was not such that he could be expected to discover the defect. In other words, the technology was so new and unfamiliar that the producer could not be expected to have recognized the defect.
[48] Article 2(1).
[49] Recital 8.
[50] For background on the retention of human tissue without relatives' consent: Learning from Bristol: The Report of the Public Inquiry into Childrens' Heart Surgery at the Bristol Royal Infirmary Cm. 5207 (2001); Report of the Inquiry into the Royal Liverpool Children's Hospital (Alder Hey) HC 12-II (2001); Department of Health The Investigation of Events that followed the death of Cyril Mark Isaacs (2003a); Department of Health Isaacs Report Response (2003); Department of Health Human Bodies, Human Choices—The Law on Human Organs and Tissue in England and Wales – a consultation report (2003).
[51] For example, the provisions dealing with appropriate consent, storage, use, discard, trafficking controlled substances, and DNA analysis of tissue.
[52] s. 54(7). Lord Warner confirmed the Government's intention during the Bill's second reading in the House of Lords: 'Cell lines are excluded from the Bill…because it applies only to human cells coming directly from a human body.': Lord Warner. 22 July 2004. Hansard. House of Lords. Column 430.
[53] Department of Health. 2003. Human Bodies, Human Choices—The Law on Human Organs and Tissue in England and Wales – a consultation report. [17.22]-[17.23]. Department of Health. 2003. *Human Bodies, Human Choices—Summary of responses to the consultation report*. [2.23].
[54] Medical Devices Agency. 2002. Code of Practice for the Production of Human-Derived Therapeutic Products. ('MDA Code').
[55] Department of Health. 2001. Code of Practice on Tissue Banks; Department of Health. 2000. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells Used in Transplantation.
[56] G. McAllister. Stem Cells and the Pharmaceutical Industry. Presentation at Stem Cell Medicine and Public Policy course, 28-29 June 2004, Hinxton, UK.
[57] See http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/Tissue/TissueGeneralInformation/TissueGeneralArticle/fs/en?CONTENT_ID=4077127&chk=8MjvZR (accessed 21/07/04).
[58] The UK Stem Cell Bank project began 1 January 2003; the Bank was officially launched and the first cell lines deposited on 19 May 2004. The Bank is sited at the National Institute for Biological Controls and Standards in Hertfordshire, UK. http://www.ukstemcellbank.org.uk/ (accessed 29/09/04).
[59] Steering Committee. 2004. Draft Code of Practice for the Use of Human Stem Cell Lines—version 1, March 2004. (Draft Code). http://www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation/public-use_of_stem_cell_lines.htm (accessed 22/07/04). Consultation period closed 28 May 2004.
[60] Steering Committee. 2004. Interim Code of Practice for the UK Stem Cell Bank—version 1, April 2004. http://www.mrc.ac.uk/index/public-interest/public-consultation/public-stem-cell-consultation/public-bank_code_of_practice.htm (accessed 22/07/04). ('Interim UK HSC Bank Code') The interim code is to be revised once the Draft Code is finalised.
[61] Draft Code [7.12], [12], [7.7].
[62] See http://www.stemcellforum.org/registries_&_banks/characterising_cell_lines.cfm (accessed 26/07/04).
[63] Draft Code [6.6]. No explanation is given for limiting the feedback options to embryo donors, and not offering them to somatic cell donors.
[64] UK Blood Transfusion & Tissue Transplantation Guidelines. 2002. 6th edition. See [23.6]. http://www.transfusionguidelines.org.uk/uk_guidelines/ukbts6_228.html (accessed 27/09/04).
[65] Draft Code [2.3], [6.3], [15.2].
[66] MRC. Research Involving Human Stem Cells: supplementary terms and conditions to be applied to new an extended MRC grounds, MRC unit programs and MRC training awards from 1/08/2003 http://www.mrc.ac.uk/pdf-terms_conditions_stem_cells.pdf (accessed 26/07/04).
[67] Draft Code [2.4], [3], [9.1], [11.1]. Strictly speaking, it is questionable whether the HFEA has legal power to make the Stem Cell Bank code binding on those who apply for its licences, since its statutory

powers apply to the creation and storage of embryos and the storage of gametes. Stem cell lines are neither embryos nor gametes. Section 1(3) of the Human Fertilisation and Embryology Act states 'this Act, so far as it governs the keeping or use of an embryo, *applies only to keeping or using an embryo outside the human body*'. (emphasis added). The HFEA is relying on a broad interpretation of its power to license embryo research. It asserts it has the power to limit how the *results* of that research can be used. By way of analogy, this is akin to an authority with power to regulate the use of apple trees exercising power over apple juice. Schedule 2(3) of the Act limits the types of research that may be licensed, but says nothing about the restrictions the HFEA may specify. The Courts might allow the HFEA wide latitude if it can establish that the restrictions are reasonably connected with showing respect for the moral status of embryos.

[68] Draft Code [9].

[69] MRC, op cit note 66.

[70] Draft Code [15.3].

[71] UK Patent Office, 'Practice Note: Inventions Involving Human Embryonic Stem Cells' (UKPO, April 2003) http://www.patent.gov.uk/patent/notices/practice/stemcells.htm (accessed 07/02/05). Totipotent embryo stem cells are not patentable because these have the capacity to develop into a human being, and hence fall foul of the prohibition against patenting the human body at a stage of its formation (Patents Act 1977, sch A2 3(a)). Processes for obtaining stem cells from human embryos are also not patentable because such inventions involve the use of a human embryo and are thus contrary to the Patent Act 1977 sch A2, 3(d).

[72] Directive 98/44/EC Art 5, 6.

[73] Edinburgh Patent (EP 94913174) EPOD 21/07/03, considering EPC Art 53(a) and rules 23d(c), 23e(1).

[74] Commercial secrets might be protected despite mandatory banking because third parties will not be granted access until depositors and accessors have agreed a Materials Use Licence: Draft Code [15.3].

[75] Art 13; Annex. The Annex suggests that if donors are to be properly informed they should be told the therapeutic purpose of procurement, consequences and risks of donation, analytical tests conducted, data recorded, levels of confidentiality, their right to access confirmed and explained results of the analytic tests, and other safeguards.

[76] Directives 65/65/EEC and 2001/83/EC (restatement).

[77] Directive 93/42/EEC.

[78] Directive 2004/27/EC recently amended the definition of medicinal products in Directive 2001/83/EC. The latest definition, reproduced here, is incorporated in UK law through the Medical Devices Regulations 2002 and the Medicines for Human Use (Clinical Trials) Regulations 2004.

[79] Directive 93/42/EEC, Art 2(a). This definition is referred to in the Medical Devices Regulations 2002 (UK). Separate definitions cover *in vitro* medical devices (98/79/EC) and active implantable devices (90/385/EEC).

[80] C. Hodges. 'European Regulation of Medical Devices'. In J.P. Griffin and J. O'Grady, 2003. The Regulation of Medical Products. London. BMJ Books; 83, 100.

[81] Directive 93/42/EEC, Art 1(5)(f), and Medical Devices Regulations 2002 (UK) s 3(d). It has been suggested that this exception was included because it was envisaged that cells and tissues of human origin would be satisfactorily covered by legislation on tissue/cell banking and blood products: Lloyd-Evans, 2004, op cit note 7, 52. The former legislation has not yet come to pass, and the latter is too narrow for recent technology.

[82] The non-biological part of the stem cell-based device might be governed by the Medical Devices Directive: Lloyd-Evans, op cit note 7.

[83] Directive 2003/63/EC.

[84] MDA code. Memorandum by the Medicines Control Agency. In House of Lords Select Committee Report on Stem Cell Research 2002 (Evidence), 256-7. The MCA advised that 'certain' stem cell products fall 'under the broad heading of "[somatic] cell therapy product".' See also EMEA Committee for Proprietary Medicinal Products. May 2001. Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products CPMP/BWP/41450/98, 10.

[85] MDA code [2.1]. See also Draft Code, 13. The MHRA can provisionally determine whether a product is a 'medicinal product'. This decision may be reviewed by the Independent Review Panel. These unusual measures indicate the degree of ambiguity surrounding the definitions.

[86] MDA code p 5, 21-22. It also recommends that evidence be collated to show 'the expected benefits to the patient' and efficacy, rather than just an absence of toxicity. The Draft Code states that

developers should demonstrate that the therapy is 'effective in delivering the expected benefit to the patient': at 14.

[87] European Commission. Proposal for a Harmonised Regulatory Framework on Human Tissue Engineered Products: DG Enterprise Consultation Paper (Brussels, 6 April 2004) p 3 http://pharmacos.eudra.org/F3/human-tissue/index.htm (accessed 07/02/05).

[88] European Commission, ibid; and Summary of Contributions. EC Regulations, as written, are community law and must be applied directly in Member State law. Directives, on the other hand, allow Member States to decide how to incorporate the objective of the directive within their own domestic legal systems. Therefore, a Regulation for tissue engineered products should "…ensure uniform and timely application of the rules…": Summary of Contributions.

[89] See http://devices.mhra.gov.uk/mda/mdawebsitev2.nsf/7d802374dabdd36600256a760041066d/6cb284dbc2cc285280256be40036dd70/$FILE/TissueEngineeringLetter.pdf (accessed 14/02/05).

[90] The Medicines for Human Use (Clinical Trials) Regulations 2004.

[91] One of us has elsewhere written on the impact of the CTR, see: S. Wallace, 2004. The Impact of the Draft UK Medicines for Human Use (Clinical Trials) Regulations 2003 on Research Ethics Committees. Ph.D. Thesis. University of Sheffield, Department of Law.

[92] E.g. the proposal for a Human Tissue Engineered-Products Regulation.

[93] The Codes and especially the EU Tissue Directive, which has legal force.

[94] The UK Stem Cell Bank does not have formal powers for inspection and monitoring. The new Human Tissue Authority will be responsible for implementing the EU Tissue Directive (if it can overcome cl 59(7) of the HTA). The government has announced plans to merge the HTA with the HFEA to create the Regulatory Agency for Fertility and Tissue (RAFT). There is some speculation that the HFEA's strict licensing (which have not been popular with IVF clinics) will influence the Human Tissue Authority. Alternatively, the merger may be a catalyst for change within the HFEA.

[95] Draft Code [8.5].

[96] The Draft Code suggests this will be reviewed at a later date: [6.2.2.4].

[97] State-sponsored initiatives such as the Regulatory Advisory Service to Bio-tech Agencies, sponsored by the East of England Development Agency, might also help SMEs adjust to the regulatory burdens in this field.

[98] The Human Tissue Bill was amended during Parliamentary debates so that the prohibition against financial payments is limited to materials intended for transplant: see HTA s 32(8)(c).

[99] This is clear from the incorporation of Good Manufacturing Practice and Good Clinical Practice in the Clinical Trials Regulations, and from recent consultation on a Human Tissue Engineered Product Regulation.

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