

MILESTONE REPORT

M 6.4.1 Stem Cell Banks, Repositories and Registries in Europe: An Overview as of May 2008

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ABSTRACT

Objective: To overview the current ethical, legal and scientific situation regarding the human stem cell banks, repositories and registries functioning in Europe, excluding cord blood banks.

Method: Review of scientific publications, legal documents and ethical guidelines in this field up through May 2008.

Result(s): The article first reviews the procedure of stem cell banking and the rules applying to it, as well as discusses the safety issues. The legal context of stem cell banking in the UK and Spain – the countries where stem cell banks are operating at present – is then presented and the missions and activities of these banks, as well as of stem cell repositories and registries functioning in Europe overviewed. **Conclusion(s):** Stem cell banking can benefit stem cell researchers and enhance international collaboration but is complicated in the context of rapidly advancing stem cell research, whereas the laws, guidelines, and ethical standards remain heterogeneous. Harmonisation of practices between stem cell line distributors to establish consistent standards is therefore needed, as well as harmonisation of international guidelines and national laws regulating stem cell banking. The creation of stem cell banks could help to achieve valuable scientific objectives as well as help meet certain ethical imperatives. The European Registry for Human Embryonic Stem Cells also adds an important global resource to advance stem cell research.

Keywords: Stem cell banks, stem cell repositories, stem cell registries, Europe

REPORT

1. Introduction

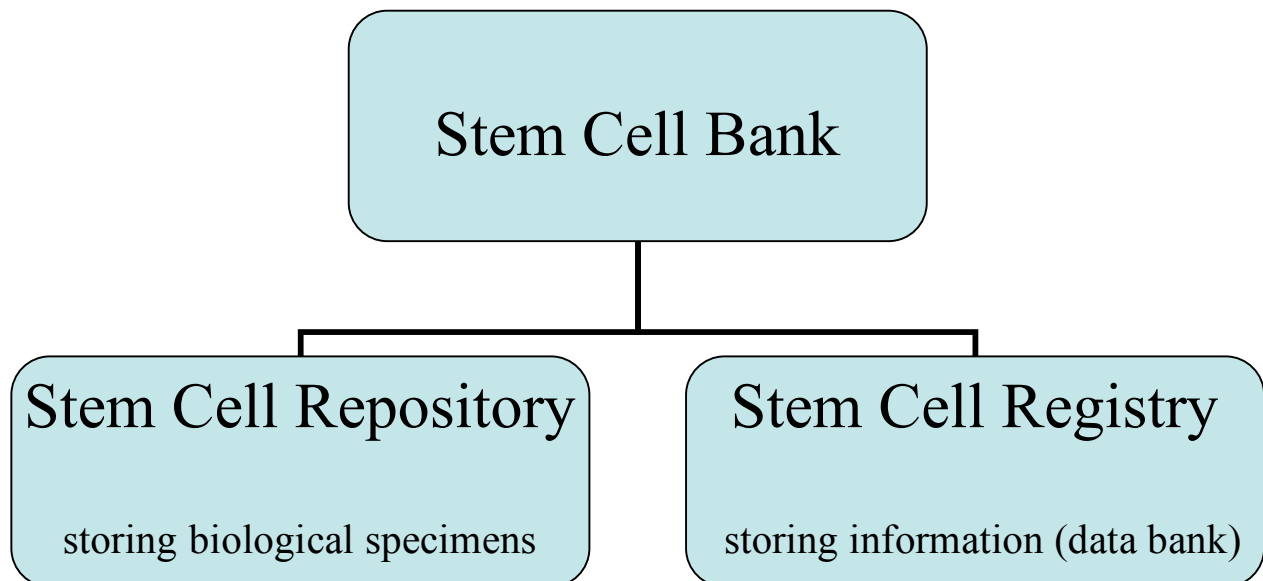
The number of research groups and projects using human stem cells has increased considerably in the last five years (1). A growing number of *in vitro* and *in vivo* studies have indicated that stem cells, known to be theoretically capable of generating all tissues of the body, may be used to treat a range of diseases or injuries by replacing and regenerating diseased or damaged tissue, as well as be valuable in gene therapy (2). However, to enable stem cells to fulfil their potential, their supply for both research and possible clinical therapies needs to be from a reliable source (2). For this purpose, banks of ethically sourced quality cell lines need to be established, cells characterised and stored under quality conditions and their safety and efficacy ensured (2).

A stem cell bank is a body composed of two different parts with two different missions: a stem cell repository, in which biological specimens are stored, and a stem cell registry, which is a data bank containing information about stem cell lines. The International Society for Stem Cell Research Guidelines (3), released in 2007, describe a stem cell bank as the institution that engages in reviewing and accepting deposit applications, assigning catalogue numbers to deposits, characterizing cell lines, performing pathogen testing, expanding, maintaining and storing human embryonic stem cell lines, performing quality assurance and quality control of all procedures, tracking distributed cell lines, and maintaining a website with pertinent characterization data, protocols and availability of human embryonic stem cell lines (3).

In the literature, the term “stem cell bank” has sometimes been used to refer to stem cell repository, less often to a stem cell registry, and often to refer to both. These different usages of the term have introduced

some confusion as to what is actually meant by a “stem cell bank”. In this article, I will use the term “stem cell bank” to refer to an entity containing both, a stem cell repository and a stem cell registry (Figure 1).

Figure 1. The composition of a stem cell bank



Creation of stem cell banks is an important step to advance stem cell research (1) by making clearly documented, ethically sourced, well characterized, safe and pure (4) stem cell lines available to both the scientific and clinical communities to promote high-quality research (2). Stem cell repositories thus face a great challenge to conserve various characteristics of the banked cells for which some of the key biological processes are not yet fully understood, and must therefore establish robust procedures to demonstrate that banked stem cell lines remain stable in culture, that key biological indicators remain intact, and that the cell line is safe to use clinically (2). Stem cell registries also face an important task of facilitating information sharing among the researchers. For example, the European Human Embryonic Stem Cell Registry (5) official website provides the information to the researchers on the existing and on the available stem cell lines worldwide. As of May 2008, in Europe the registry listed 17 embryonic stem cell lines existing in Belgium, 7 in the Czech Republic, 21 in Denmark, 10 in Finland, 12 in Israel, 4 in the Netherlands, 8 in Spain, 1 in Switzerland, and even 64 in Sweden and 83 in the UK, with different rates of their availability for researchers in different countries (5).

The aim of this article is to overview the current situation regarding human stem cell repositories and registries functioning in Europe. The review of cord blood banks falls outside of the scope of this article, as cord blood banking raises many specific issues which had better be dealt with separately.

The stem cell banking procedure is explained and the safety issues in stem cell banking discussed. The article further presents the context in which stem cell banking in Europe takes place – the changing legislative climate of European countries regarding human embryonic stem cell research – as well as the stem cell banks functioning in European countries, their missions and objectives. The stem cell registries operating in Europe are also overviewed.

2. Procedure of Stem Cell Banking

The International Society for Stem Cell Research has released international nonbinding guidelines on human embryonic stem cell research, compiled by researchers, ethicists and legal experts from 14 countries, to encourage uniform research practices worldwide (6). The Guidelines, along with individual academics specialized in the field, suggest the following necessary or sufficient conditions for establishing and running a stem cell bank:

1. That stem cell banks are accredited and that they implement a strict regulatory framework of good manufacturing and laboratory practices as well as a quality system complying with international quality systems standards (1);
2. That stem cell banks ensure that derivation of new pluripotent stem cell lines is scientifically justified and executed by scientists with appropriate expertise (3);

3. That stem cell banks encourage early deposit of lines into centralized repositories where the lines will be held for release and distribution upon publication, and make new lines generally available as soon as possible following first publication (3);
4. That stem cell banks prepare detailed process maps for all activities undertaken in the bank in order to identify clearly all the steps in critical procedures and ensure that the entire process from deposition of cells to provision to recipient is properly controlled and documented to ensure, as far as possible, a reproducible product (2, 3).
5. That repositories form and adhere to common methods and standards, and therefore establish their own publicly available guidelines (1, 3) as well as protocols for deposit, storage and distribution of human embryonic stem cell lines and related materials (3);
6. That stem cell banks collect, store and make publicly available the following documentation:
 - a. proof of institutional approvals of the procurement of research materials according to ethical and legal principles as well as protocols for derivation of new lines (3),
 - b. donor informed consent documents and what, if any, reimbursement of direct expenses or financial considerations of any kind were provided to the donors (3),
 - c. as much donor information as possible (3, 7) along with the cell line (including ethnic background, medical history, infectious disease screening) in order to enable future potential therapeutic applications, at the same time protecting the privacy of donors and donor information (e.g. by applying internationally accepted standards of anonymization and coding) (3),
 - d. all technical information from depositor (7) (e.g. protocols used in the derivation of lines, culture conditions, infectious disease testing, passage number and characterization data as well as any modifications in depositor's protocols or new information obtained by the repository) (1, 3), because the origin of the cell lines can have an important effect on their quality (8).
7. That the cell lines are distributed internationally and that only the necessary costs are charged (including shipping and handling) (3).

The procedure of cell banking involves the following stages:

1. **Receiving cell material into the Bank.** On arrival at the Bank, the cells are placed in frozen storage in quarantine until pre-banking safety criteria are met (1);
2. **Producing Pre-master Cell Bank.** Once the cell lines have been obtained from a reliable source and the safety criteria have been met, it is important to establish a pre-master bank at the earliest stage and apply appropriate tests to rule out microbiological contaminants (1). Pre-master bank is a limited bank of cells, most of which are used for further quality assurance and safety tests to establish the characteristics of the cell lines at the time of deposit (many of these tests are common to all cell lines but others are specific to particular cell lines) (2, 9). Material from this bank is cryopreserved as a long-term archive (9). It is very important that the depositors also transfer the protocols used for the cell culture, especially the protocols for freezing and thawing, the use of feeder or extracellular matrix, the culture medium used, when to carry out the passages, and the way in which to carry them out (1). The transfer of protocols is essential because at present there is no standardization, and the conditions and culture mediums are specific for each human embryonic stem cell line (1).
3. **Producing Master Cell Bank,** which is formed of cryopreserved cells from the Pre-master Cell Bank after performing quality assurance and safety tests (2, 9). These stem cells are a reference point for all future work undertaken with the given cell line (9). From this Bank all future cell banks are prepared, and therefore it undergoes extensive characterisation and quality control testing, including:
 - a. cytogenetics (1),
 - b. DNA profiling (9), which can help to establish small differences among cell lines that can underlie their particular properties and potential (10),
 - c. isoenzyme analysis,
 - d. morphological assessment,
 - e. analysis of surface and other recognised molecular markers,
 - f. measurement of growth characteristics (1),
 - g. viability and functional assessments (9), which should be done before freezing cells and after thawing cells in order to know the cell recovery rate and the good management of the protocols (this test is performed in pre-master, master, and distribution banks) (1),
 - h. sterility tests for microbial, mycoplasma and certain types of microorganism contamination (9). There are numerous types of microorganisms that may contaminate cell cultures and remain undetected without specific isolation methods (1). In order to isolate such microorganisms

different culture and conditions should be required for their detection and scientists should be aware of the potential for rare contamination of this type (1),

- i. tests for viral contamination (9), as some cell lines may contain endogenous viruses, be contaminated with exogenous viruses, secrete viral particles or express viral antigens on their surface (1).

The cells stored in the Master Cell Bank are not distributed so that there will always be a bank of cells with known characteristics (9).

4. **Producing Distribution Banks** from the Master Cell Bank. The Distribution (or working) Cell Bank is a large bank of cells prepared from a single or limited number of ampoules of the Master Cell Bank (9). Cells from this bank are distributed and used for experimental or manufacturing purposes (9). Extensive testing is performed on the stock of this bank to ensure its comparability with both previous kinds of banks (9). Once this bank has been exhausted, a fresh Distribution Bank can be prepared from material within the Master Cell Bank (9).

Such a tiered banking system ensures that cells from the same passage level are available over many decades (2, 9). Segregation of fully tested cell banks from partially tested and untested banks is ensured by physical separation of cell banks in liquid nitrogen storage refrigerators (2).

3. Safety issues in stem cell banking

The European Union Good Manufacturing Practices related to validation, screening, processing, storing, and delivering stem cell lines to the users (11) require that stem cell banks also comply with these practices and produce the cells under the same rules that apply to pharmaceutical manufacturers for the cells to be suitable for future clinical use (1). Therefore a stem cell bank should be constructed and operated to minimise the introduction, generation and retention of particles and micro-organisms, as well as be equipped with clean rooms with monitored environmental controls to minimize microbial and particulate contamination (1). The equipment used should also be maintained and calibrated to make sure that the accepted criteria of quality are met (1). The European Human Tissues and Cells Directive 2004/23/EC enforces such requirements for environmental control starting April 2006 (12). Among other things, stem cell banks are responsible for assuring the quality and biosafety of the cells used in novel medical therapies (13). To achieve this, the EU Directive requires to standardise and validate the processes and procedures involved and to introduce effective and stringent quality assurance programmes (12).

Environmental monitoring. Environmental monitoring provides assurance that the cells have been produced in an appropriate environment to minimise risk of infection to patients (13). An environmental monitoring program involves procedures which assure that the cell processing from an environmental perspective is maintained within the established limits for air particles, microbial air contamination and contamination of operators and surfaces (13). A formal program of environmental monitoring should function in each stem cell bank to specify and assess key factors and their influence on the microbiological quality of the process and product, as well as depend on local conditions in each cell bank (each centre evaluates its specific needs and establishes appropriate, non-intrusive, monitoring procedures) (13). The stem cell bank should receive additional environmental control tests after, for example, corrective actions following a non-compliance, a change of specifications of the installation or use for a particular area, or after a prolonged period outside of the normal operational mode (13). In the environmental monitoring programme, the following aspects need to be assured:

1. **Appropriate air quality for cell banking activities.** The processing of stem cell lines for application in human therapy requires a physical environment in which air quality (the number of airborne particles) is controlled to minimize risk of contamination (13). In a clean room area, the levels of air cleanliness, differential pressure, and temperature must be specified and other environmental parameters, such as relative humidity and levels of sound or luminosity, should also be maintained within certain limits (13). Monitoring and control may be achieved by direct manipulation by appropriate staff or thorough specialised software installed in a building management system which can only be corrected by authorised personnel (13). Environmental conditions may be specified for the "at rest" state when the equipment is functioning but no personnel is present and for the "operational" state when the facility is functioning with a specified number of personnel working (13).
2. **Microbial monitoring of surfaces.** If performed on a regular basis, such monitoring can provide a valuable estimate of the level of contamination on surfaces like floors, walls and work surfaces and equipment (centrifuges and incubators) (13).

3. **Testing for human and animal pathogens.** Stem cell repositories should screen all processed cells for serious human and animal pathogens and assure that no contaminants are introduced in the banking procedures, including storage, as such pathogens present a risk to other processed tissues or cells, staff and future recipients (1).
4. **Testing antibiotic sensitivity.** In certain circumstances, it may also be necessary to carry out antibiotic sensitivity tests, especially where products have been contaminated as part of the validation of the new installations, products and procedures, or where resistance to disinfectants is observed (13).
5. **Monitoring of personnel.** It is also important to ensure that all personnel (even those who are in charge of cleaning and maintenance) employed in a stem cell bank receive regular training in personal hygiene and get informed about sources of laboratory contamination (13). It may be equally important to provide training in basic microbiology required for performance of environmental testing procedures for the aseptic manipulation of therapeutic products (13). Staff showing signs of infection or returning to work from a period of being sick with certain diseases represents a direct risk to cell culture work, and this risk should be monitored (by the use of agar plate culture of finger digit and glove impressions) and evaluated before starting critical cell processing work (13).
6. **Checking the suitability of the culture media.** The culture media used should be in accordance with the national recommendations as well as the recommendations for appropriate cell product (13). If an alternative or supplementary media is used for sustaining the growth of a specified range of micro-organisms, validation studies should be performed to show that such media is suitable (13).
7. **Keeping records of microbial identification.** It is important to keep records of the number and type of isolated micro-organisms to facilitate the early detection of trends, such as repeated isolation of a common species of micro-organisms in different areas and repeated isolation of a single species in the same location (13). The identification of the micro-organisms can help indicate the possible sources of infection as well as determine the methods of control (13).
8. **Collection and analysis of data** is an integral part of an environmental monitoring program and is crucial for setting alert and action limits (13). Statistical methods can be used to monitor data trends and to interpret environmental monitoring data (13).

Environmental monitoring should be robust, readily interrogated for trend analysis and cost effective (13). However, it should not become overburdening on staff and testing should not be so rigorous so that it would interfere with cell processing through excessive interventions into the work of the staff and in this way put the quality of the final product at risk (13).

Framework of limits of action and alert. Each clinical cell banking centre should establish its own alert levels (levels of contamination, usually based on historic data, that surpass the established limits but which assure that the process is still controlled) and action limits for critical processing areas (13). If alert levels are surpassed, the cause of an unusual result should be investigated (13). The alert limit provides a warning signal about the current operational conditions and immediate investigation as well as appropriate corrective actions should be taken (13). Both alert and action levels should be defined in standard operational procedures (13).

Safety tests. The risk of contamination increases when cell lines are maintained for long periods in culture medium, which supports the growth of bacteria and fungi (9). The routine use of antibiotics to suppress growth may also have adverse effects on the cells (9). Contamination from the laboratory environment can be monitored by routine screening for bacteria, fungi, yeast, and mycoplasma, viruses, sterility and adventitious agents according to the European Pharmacopoeia tests (14–16), which should be used for regular quality control in the premaster, master, and distribution banks (17). The banks should also assure traceability of stem cell lines if they are to be used in possible therapeutic applications (17).

For clinical grade cells, an extensive set of tests for adventitious agents must be performed based on the risk assessment (2). The need for testing feeder cells of human embryonic stem cell culture for agents possibly introduced from non-human feeder layers used in the growth of many embryonic stem cell lines (2), has to be reviewed on a case by case basis (1, 2). For example, bovine serum necessary for cell culture may be contaminated with viruses of animal origin, that could further be transmitted to the recipients (1), and European guidelines describe the screening of bovine serum before its use in the manufacturing of a human biological product (18). The European regulatory agencies (19) have identified a risk assessment for transmissible spongiform encephalopathies in all products derived from ruminants, and suggest to perform tests for the agents of transmissible spongiform encephalopathies in addition to routine precautionary measures, when such tests are proven to be reliable (19). Embryonic stem cell lines derived

with mouse or human feeders can also transmit infectious microorganisms to the recipient (20), therefore such feeder cells must also be screened for a wide spectrum of viruses, which cause serious human diseases (1).

Quality assurance tests are also important and consist of the following tests:

1. **Viability tests** developed to supplement the routine methods of assessment currently used in most cell banks;
2. **DNA fingerprinting** authenticates each line in order for depositors and users to be confident that the lines are *bona fide* and are not cross-contaminated with pre-existing cell lines;
3. **Investigating epigenetic changes** which may cause subtle changes in the characteristics of the stem cells;
4. **Phenotyping of cells** using a panel of well-defined antibodies, selected by experts in the field, and tailored to each line;
5. **Assessing the stability of stem cell lines in culture** by performing comparisons between the lines stored in different banks (Pre-Master, Master, etc.) of a stem cell bank;
6. **Exploring the robustness of stem cell culture procedures** to facilitate standardization, since each line may be expected to have its own set of unique procedures for growth and preservation;
7. **Ensuring traceability** of cells intended for clinical use in humans (2).

Data protection is also an important safety issue in stem cell banking, especially regarding stem cell registries. Stem cell banks and registries must make sure that any personal information, needed for traceability of stem cell lines and related products, is properly protected according to the requirements of the European Union Directive 95/46/EC (21).

4. European legal provisions and ethical guidelines relevant to stem cell banking

There are several legal and ethical documents directly relevant to stem cell banking activities in the European countries. Therefore it is important to overview the regulatory context in which stem cell banks operate, before discussing their missions and activities. This chapter will thus briefly review such regulatory documents.

EU Tissues and Cells Directive 2004/23/EC and its implications for stem cell banking. The Directive went into force in April 2006, and covers human haematopoietic, umbilical cord and bone marrow stem cells, reproductive cells (eggs, sperm), foetal tissues and cells, as well as adult and embryonic stem cells human tissues and cells, but does not apply to organs nor to *in vitro* research or research in animal models (12). It regulates donation, procurement, testing, processing, preservation, storage and distribution of such tissues and cells and applies to research for the purposes of application to the human body (12). The aim of the Directive is to lay down standards of quality in order to ensure a high level of protection of human health, and a key principle of this Directive is the requirement of traceability of human tissues and cells from donor to recipient and vice versa in order to make it possible to verify the compliance with quality and safety standards (12). Researchers must ensure that it is possible to trace cryopreserved stem cell lines to the primary cells and the donated human tissue, and must ensure that an anonymised link is in place for the purposes of traceability (12, 22). The Directive also requires that each cell line should be given a unique identifying number that must preserve donor anonymity and be used in all procedures and publications (12).

Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC (23) implements certain provisions of the Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, and sets the requirements for the accreditation, designation, authorisation or licensing of tissue establishments, as well as of tissue and cell preparation processes (23). It also provides the rules for the notification of serious adverse reactions and adverse events as well as prescribes the communication of information between competent authorities (23). The Directive requires that tissue establishments have effective and accurate systems to uniquely identify and label received and distributed tissues and cells and retain for at least 30 years the specified data necessary to enable traceability (23). It also requires that a single European identifying code is allocated to all donated material to ensure proper identification of the donor and the traceability of donated material and to provide information on the main characteristics and properties of tissues and cells (23).

Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC (24) sets the requirements for accrediting, designating, authorizing or licensing the procurement of human tissues and cells as well as the selection criteria and laboratory tests required for donors (24). The Directive also regulates tissue and/or cell donation and procurement procedures as well as their reception at the tissue

establishment, and sets the requirements for direct distribution to the recipient of specific tissues and cells (24).

EU Data Protection Directive 95/46/EC regulates the protection of the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data (21). It applies to the processing of personal data wholly or partly by automatic means, and to the processing otherwise than by automatic means of personal data which form or are intended to form part of a filing system (21). The Directive requires that, among other things, Member States ensure that personal data is processed fairly and lawfully, collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes (further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that appropriate safeguards are in place) and that the data is kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed (21). The Directive further requires that, among other things, the Member States prohibit the processing of personal data revealing racial or ethnic origin, or concerning health or sex life, except in the cases where the data subject has given his explicit consent to the processing of those data, unless the laws of the Member State provide otherwise (21). The Directive also regulates the security of data processing and requires the Member States to implement appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing (21). Furthermore, it requires that such measures ensure a level of security appropriate to the risks represented by the processing and the nature of the data to be protected (21).

EGE Opinion on Funding of human embryonic stem cell research in the 7th Framework Programme.

The EU's 7th Framework Programme, adopted on 24 July 2006 by the European Council after intense political discussions and the opposition from certain countries' politicians who, for ethical and moral reasons, remained firmly against such decision, allows human embryonic stem cell research under certain conditions: for example, no activity is to be funded that is forbidden in all member states, and research projects are only considered for funding from member states where the proposed research is legal (25). The European Group on Ethics in Science and New Technologies (EGE) has recognised the need to promote responsible research that is transparent, serves the public interest, respects Member States' autonomy, preserves public trust, promotes international cooperation and requires the embedding of ethics within research practice (25). The Group has suggested that, among others, the following considerations have to apply to human embryonic stem cell research funded by the EU 7th Framework Programme:

1. The human embryonic stem cell lines have to result from non-implanted IVF embryos;
2. The human embryonic stem cell lines listed in the European Registry should be used where possible;
3. If alternatives to human embryonic stem cells with the same scientific potential as embryo-derived stem cells appear, their use should be maximised;
4. Donors' rights (in terms of health, informed consent, data protection and free donation) have to be protected and safeguarded;
5. Actions to stimulate public debate on this research area are needed at the EU level (25).

The EGE opinion is not a binding document, like the EU Directives are (which are transposed to the national laws of the Member States, with a certain liberty in their national interpretation and implementation), but it is likely to have an impact on the review procedure of research applications in the European Commission.

5. The legal context of stem cell banking in the UK and Spain – home of the three stem cell banks operating in Europe

The legislative climate in the European countries regulating human embryonic stem cell research is very diverse and reflects Europe's historic pluralism as well as different ethical, religious, philosophical and political positions in different countries (5). Such diversity is also due to the lack of a commonly accepted definition of the moral status of a human embryo. The legislative climate directly affects stem cell banking: For example, the legislation change in Spain in 2003 towards more permissive regarding embryonic research and the creation of new legislation regarding stem cell research has enabled the creation of two stem cell banks in Spain. As of May 2008, the following countries have specific permissive legislation with regard to human embryonic stem cell research and somatic cell nuclear transfer: Belgium, Israel, Sweden, UK, Spain, Finland and the Czech Republic permit human embryonic stem cell research, the derivation of new human embryonic stem cell lines from spare IVF embryos and somatic cell nuclear transfer by law (however, the legislation of Finland and the Czech Republic neither prohibit nor allow somatic cell nuclear

transfer) (5). Portugal has just passed a new law (26), which requires additional conditions to be clarified (26). This is not yet done at the time of writing this paper, but the law may open up more possibilities for research in this area (26).

It is in the countries with the permissive legislation that the three stem cell banks so far operating in Europe have been established: the UK Stem Cell Bank (27) – the first of its kind in the world – and the two stem cell banks in Spain: the Andalusian Stem Cell Bank (28) and the Barcelona Stem Cell Bank (29). This chapter will further present the legal situation in the UK and in Spain related to stem cell banking, and the following chapter will provide an overview of the missions, objectives, activities and organisation of these stem cell banks.

5.1 The United Kingdom

The Human Tissue Act 2004 and its implication for stem cell banking. The UK Human Tissue Act was implemented on 1 April 2006, and it regulates the collection and storage of human tissue, including body parts, organs, tissue, blood etc (broadly anything consisting of or including human cells) from the living or deceased (30–32), with exception of hair and nail of a living person, and gametes and embryos (22), which are separately regulated by the Human Fertilisation and Embryology Act 1990 (33). Established cell lines as well as any other human material created outside the human body (22) as well as subcellular material such as proteins fall outside the scope of the Act, but the Act applies to stem cells (not cell lines) stored for more than 48 hours (34). The Act makes informed consent a fundamental principle of lawful storage and use of body parts, organs and tissue from the living or the deceased (30–32), but is not retrospective regarding consent: It is lawful to keep and use tissue samples without consent if they were held before 1 September 2006 (30, 32).

However, this does not apply to the licensing provisions – there is no exemption for material collected prior to the Act coming into force (34). The Act requires a license for a number of activities, including storage of human tissue (30, 32). The license is needed for removing and storing tissue for the primary purpose of research and distribution to other researchers (tissue bank), but not required if the material stored was created outside of the human body, for example, a cell line or cell culture (30, 31, 34) where none of the original cells are present or the material has undergone a process to render it non-cellular (34). The license is also not required for specific research projects with ethical approval where the researcher cannot link the tissue to the patient (30, 32). This does not mean, however, that samples must be permanently and irrevocably unlinked – linking can be made through a third party, which may make the material anonymous and pass it on to the researcher (34).

The consent provisions of the Human Tissue Act 2004 do not apply to imported material, but the licensing provisions of the Act do apply to imported material therefore storage of imported relevant material for research other than a specific ethically approved project or a project pending approval requires a license (34).

Among other requirements, the Act also demands that proper records and documentation for all tissues and organs acquired and/or passed on to others are maintained, starting with the establishment where the material is removed from the body (30, 32). The Act makes carrying out licensable activity without a license an offence (30, 31).

The Human Fertilisation and Embryology Act 1990 and its implications for stem cell banking. This Act regulates research on human embryos in the UK and makes it an offence to carry out such research without a license prescribed by the Act. A license may be granted only if the use of embryos is necessary for the proposed research project and the research itself is necessary for the following purposes:

1. To promote advances in the treatment of infertility;
2. To increase knowledge about the causes of congenital disease;
3. To increase knowledge about the causes of miscarriages;
4. To develop more effective techniques for contraception;
5. To develop methods for detecting the presence of gene or chromosome abnormalities in embryos before implantation;
6. To pursue other purposes if such are specified in the regulations (33).

It is a condition of a license that a sample of all human embryonic stem cell lines derived in the UK must be deposited in the UK Stem Cell Bank (22, 33). Licensees are also not permitted to carry out secondary research projects on embryonic stem cells or to transfer embryonic stem cell lines to third parties without the approval of the Steering Committee for the UK Stem Cell Bank (22, 33). Stem cells taken from an

embryo are no longer the subject of regulation by this Act with the exception of the requirement to fulfill conditions of the license as described above (22, 33).

The Human Fertilisation and Embryology (Research Purposes) Regulations (35) were enacted in 2001 and extended the purposes for which an embryo could be created for purposes other than reproduction, if such research was needed to fulfill the following aims:

1. To increase knowledge about the development of embryos;
2. To increase knowledge about serious disease, or
3. To enable any such knowledge to be applied in developing treatments for serious disease (35).

The Human Fertilisation and Embryology (Quality and Safety) Regulations 2007 (36), amend the Human Fertilisation and Embryology Act 1990 and implement, in relation to gametes and embryos intended for use in a human recipient, the Directive 2004/23/EC and the Directives 2006/17/EC and 2006/86/EC, which lay down technical requirements in relation to Directive 2004/23/EC. The Regulations impose safety and quality requirements in relation to human tissue and cells intended for human application, including stem cells and cell lines grown outside the body, and excluding reproductive cells, embryos outside the body, organs and blood (36).

Code of Practice for the Use of Human Stem Cell Lines and its implication to stem cell banking. The Code provides guidance on best practice for those working with stem cell lines and specifies oversight mechanisms for research involving human embryonic stem cell lines (22). Besides many other regulations, the Code outlines the steps for the accession of stem cell lines from the UK Stem Cell Bank, requires free and informed consent and provides a list of criteria that must be addressed in information leaflets and consent forms provided by IVF clinics for the donation of embryos for stem cell research (22). The Code also suggests that the research projects for which human embryonic stem cell lines are used have been subjected to scientific peer review (but does not make such review a pre-condition for stem cell line access approval), requires Research Ethics Committee approval for research in human tissue, for clinical trials of all stem cell derived therapeutic products and as part of the application procedure for an Human Fertilisation and Embryology Act-required license, but does not demand such approval for research involving established human embryonic stem cell lines (22). The Code also states that the ownership of any intellectual property embodied in stem cell lines curated by the Bank remains with the originator of these lines, and they can only be released by the Bank if a Material Use License between the depositor and accessor is in place setting out the rights of exploitation and ownership of any intellectual property arising from the research conducted by the user (22). Regarding safety issues, the Code requires that those working with stem cell lines follow the general principles of Good Research Practice of the Medical Research Council, 2000 (37).

The UK Stem Cell Bank is overseen by the Stem Cell Steering Committee, which, before accepting stem cell lines for deposition in the Bank, has to satisfy itself that these have been ethically sourced, with fully informed donor consent, and that they are a valuable resource for the biomedical research community (22). The Steering Committee encourages the deposition into the UK Stem Cell Bank the human embryonic stem cell lines derived outside the UK as well as somatic stem cell lines derived in the UK or abroad as long as they fulfill the criteria of informed consent and value to the research community (22). The Steering Committee expects that human embryonic stem cell lines are only used for justified and valuable purposes that reflect the following requirements:

1. Research which increases the knowledge about the development of embryos or has the long term goal of helping to increase knowledge about serious diseases and their treatment;
2. Basic cell research which underpins these aims;
3. Development of cell based therapies for clinical trials in respect of serious human diseases (22).

Although the Steering Committee expects the UK Stem Cell Bank to be the preferred source of stem cell lines it is not a requirement that lines are exclusively accessed from the Bank, as there may be occasions when researchers access human embryonic stem cell lines from other sources. However, all researchers wishing to work with human embryonic stem cell lines (whether accessed from the Bank, from other sources in the UK or overseas) should inform the Steering Committee which needs to satisfy itself that the human embryonic stem cell lines have been ethically sourced with fully informed and free donor consent (22).

Although this Code of Practice should be regarded as an evolving interim document which will be revised and updated in line with practice (22) and requirements arising from the Human Tissue Act and the EU Tissue Directive, critical comments, related to the Code, have been raised by Morgan, Thomson, Brownsword, Brownsword, Halliday, Grubb et al. (38) in the article published in Legal Studies in 2007

regarding the lack of foresight and jurisdictional uncertainties in the regulatory interface between the Human Fertilisation and Embryology Authority, the Stem Cell Bank, and beyond (38).

5.2. Spain

The Law 45/2003 of 21 November 2003 amending Law No. 35/1988 of 22 November 1988 on assisted reproduction procedures allows the fertilization of maximum three oocytes in the same cycle and the transfer to a woman of only three pre-embryos in each cycle. When surplus pre-embryos are generated in exceptional cases, they may be cryopreserved for a period equivalent to the fertile life of the woman concerned, with the objective of transferring them to her for subsequent attempts (39).

Crown Decree 2132/2004 of 29 October 2004 lays down provisions regarding surplus pre-embryos frozen prior to the entry into force of Law 45/2003 of 21 November 2003. It determines the specific conditions under which biological structures obtained at the time they are thawed may be used for research purposes (40). The conditions include the consent of progenitors to the use of pre-embryos for research purposes and the submission of a favorable report by the National Centre's Commission for the Monitoring and Control of the Donation and Use of Human Cells and Tissues prior to the commencement of a research project (40).

More recently, the **Order SCO/393/2006 of 8 February 2006** provides for the organization and operation of the National Bank for Cell Lines (41) and the **Law 14/2006 of 26 May 2006** on assisted human reproduction procedures regulates, among other areas, the use of pre-embryos cryopreserved before the entry into force of the law and control of the donation and use of human cells and tissues (42).

The most recent piece of legislation is the **Law 14/2007 of 3 July 2007** on biomedical research (43) which, among other areas, regulates the procurement of embryonic cells. This law prohibits the creation of human pre-embryos and embryos solely for experimental purposes (43) but permits the use of any technique for obtaining human stem cells for therapeutic or research purposes, including the activation of oocytes through nuclear transfer, under the terms laid down in this law, provided that it does not entail the creation of a pre-embryo or embryo solely for this purpose (43).

6. Stem cell banks in Europe

To date, there is no one centralised European stem cell bank, but there are three national stem cell banks in Europe:

1. **The UK Stem Cell Bank** (27), established in 2003 at the National Institute for Biological Standards and Control (UK government scientific institute experienced in ensuring public health through the standardisation and control of biological products used in medicine) (44) and accredited in June 2004 (2, 9);
2. **The Barcelona Stem Cell Bank**, a functional unit of the Centre of Regenerative Medicine in Barcelona (29);
3. **Andalusian Stem Cell Bank** at the Andalusian Molecular Biology and Regenerative Medicine Centre, a multidisciplinary biomedical research centre in Andalusia, and aiming to transforming the results of the scientific work carried out in the Centre into direct improvements to citizens' health and quality of life (28).

This chapter will present each of these stem cell banks in greater detail.

6.1. The UK Stem Cell Bank

The UK stem cell bank is a pioneer bank in Europe, which has proposed the grounds on which a bank should be established and a program of research that improves the banking of stem cells including cryopreservation and cell characterization (1, 2). The UK Stem Cell Bank (27) is a national bank for stem cell lines and is committed to working closely with the clinical and research communities to provide qualified stocks of human stem cell lines of adult, foetal and embryonic origin for both research and for use in emerging human therapy (2). The Bank does not only provide support on cell banking issues, but also advises companies developing new products on quality and safety issues (2). The Bank is funded by the UK Medical Research Council and the Biotechnology and Biological Sciences Research Council (9). The establishment of a national stem cell bank was expected to minimise the number of embryos used for stem cell derivation by providing high quality banks of stem cells that would be freely available to the scientific

community (9). The UK laboratories deriving human embryonic stem cell lines are therefore required to deposit a sample of their line(s) in the Bank as a formal requirement for granting their licence (9). However, it is too early to say what effect this Bank will have on the number of embryos used for stem cell derivation (9). As of May 2008, the Bank contains 49 embryonic stem cell lines (5), 11 out of which are available for researchers (5).

Depositing cells. The Steering Committee examines all applications to deposit cells in the Bank in order to ensure that these have been ethically sourced with fully informed consent and that the cell lines represent a valuable resource for the biomedical community (9).

Aims. The Bank has the following aims:

1. To enable researchers to access stem cell lines derived from adult, foetal and embryonic sources for the study of stem cell biology and related research and development;
2. To provide the researchers working on the development of therapeutic applications with stem cell lines from clinical grade cell banks;
3. To enable the recipient to reproduce stem cell lines in their laboratory, the bank works closely with depositors of cell lines in order to capture and document the procedures and conditions under which cell lines are cultured, preserved and characterised (2).

Activities. The Bank encompasses a spectrum of varied activities, including:

1. Establishment of well-characterised and reliable banks of stem cell lines of embryonic, foetal and adult origin, available to researchers in the UK and elsewhere (2, 9);
2. Provision of cell banks as starting materials appropriate for clinical use (2, 9);
3. Ensuring appropriate safety testing adapted for research and clinical grade cells (2, 9);
4. Demonstrating that the cell banks prepared by the UK Stem Cell Bank are consistent with the characteristics of the cell lines as identified by the depositor (2, 9);
5. Assessing the performance of the cell lines at different passage levels during extended periods of culture to ensure that they retain their suitability for their intended application (2, 8);
6. Disseminating performance data relating to the cell lines and developing best practice in their culture, safety testing, characterisation and preservation (9);
7. Ensuring that necessary rules are in place to enable unhampered research whilst protecting the intellectual property of the depositors (2);
8. Supporting training about the culture, preservation and characterisation of stem cells (2).

Production. The Bank produces both *research grade* stem cell lines (lines which will be used for research purposes) and *clinical grade* stem cell lines (those that in the future will provide material for clinical trials and therapies) (2). The EU Tissues and Cells Directive 2004/23/EC (12) requires that human embryonic stem cells intended for clinical application meet the requirements not only of the parent directive but also of its technical annexes (45, 46). In the UK Stem Cell Bank, the standards applied to the banking of *clinical grade* stem cells are also applied to *research grade* stem cell lines (9). The difference lies mainly in the stringent safety testing which will be applied to *clinical grade* cell lines and the requirement under the EU Tissues and Cells Directive for an appropriate level of donor information for clinical assessment, when the Bank releases a cell line for clinical application (9).

Management. The Bank is managed by the Steering Committee, which was set up by the UK House of Lords and is composed of senior representatives of various regulatory bodies, such as Medicines and Healthcare Products Regulatory Agency, the Human Fertilisation and Embryology Authority or the National Blood Service, as well as key research groups, ethicists and legal advisory groups (2). The Steering Committee has developed a Code of Practice for the Use of Human Stem Cell Lines (22) with which the Bank has to comply. This Code of Practice for the Use of Human Stem Cell Lines is regarded as an evolving interim document which will be revised and updated in line with practice (22), and requirements arising from the Human Tissue Act 2004 (30), that came into force on 1 April 2006, and the EU Tissues and Cells Directive (12). As a future participant in the generation of cells for clinical therapies, the Bank must also comply with the current Department of Health guidelines for UK tissue banks (47).

Dealing with conflicts of interest. The employees of the UK Stem Cell Bank are required to remain independent and free of any conflicts of interest, and therefore to refrain from any involvement in commercial product development or basic research into stem cell biology (2).

Scientific collaboration. The UK Stem Cell Bank is committed to establishing a programme of research that improves the banking of stem cells including cryopreservation and cell characterisation (2).

Communication, training, and education. The UK Stem Cell Bank has a close connection with many partners in the scientific community both in the UK and abroad and aims to respond to the needs of both users and depositors (2). The Bank is establishing links with expert centres around the world as well as with national and international stem cell research networks, and the members of the Bank are actively engaged in a programme of communication of its aims and purposes (2).

6.2 The Barcelona Stem Cell Bank

Aims. The Barcelona Stem Cell Bank aims to:

1. Develop research activities in the area of regenerative medicine and embryonic development; (especially study human embryonic stem cell development in the conditions free from animal-origin products, as well as adapt stem cell derivation methodology to an animal-origin-free system, so that derived stem cells may be useful for clinical applications);
2. Produce stem cell material suitable for use in clinical research (29).

Activities. As of May 2008, the Bank contains 5 embryonic stem cell lines (5, 29). The Bank performs the following activities with the human embryonic stem cells:

1. Derivation (e.g. derive new stem cell lines from genetically abnormal embryos, and use the derived lines as models for corresponding pathologies);
2. Maintenance;
3. Characterisation (e.g. *in vivo* characterization of stem cell differentiation potential to assure the biological properties of the *in vitro* cultures);
4. Preservation (29).

6.3 Andalusian Stem Cell Bank at the Andalusian Molecular Biology and Regenerative Medicine Centre

The Andalusian Molecular Biology and Regenerative Medicine Centre is a multidisciplinary biomedical research centre in Andalusia, drawing together basic and applied research (29). The Andalusia Stem Cell Bank, founded under the auspices of this Centre, was the first public body of its type (specifically for research into stem cells) to be created in Spain (48). The bank opened in late January 2004 at a public university hospital in Granada, after the regional government of Andalusia had invested more than 600 000 Euros in laboratories and other equipment for this bank (48). The aim of the Bank is to transform the results of the scientific work carried out there into direct improvements to citizens' health and quality of life (29). The bank screens, cultivates and stores legally authorized embryonic stem cell lines (48, 49).

7. Stem Cell Registries

The mission of a centralised stem cell registry is to provide vital information regarding the human stem cell lines held by different entities, and such transparency facilitates access to and sharing of human embryonic stem cell lines (4). Unlike a stem cell bank, a registry does not manage the complex logistics of maintaining, processing and distributing human embryonic stem cell lines (4). The aims of stem cell registries are:

1. To accelerate scientific progress and improve global practice in stem cell research by enhancing international collaboration and information sharing;
2. To encourage standardized benchmarking for the derivation and handling of human embryonic stem cell lines by propagating open disclosure;
3. To inform the scientific community of the various standards being applied to stem cell research (4);
4. To help ensure that data generated by different laboratories using the same cell lines are comparable, reproducible and consistent (7).

There are several stem cell registries operating in Europe, and this chapter will provide the overview of each of them.

7.1. The European Human Embryonic Stem Cell Registry

Funders and participants. Already in 2000, the European Group on Ethics (EGE) proposed that stem cell banks should be regulated at a European level. The European Human Embryonic Stem Cell Registry has been funded as a Specific Support Action under the "Life Sciences, Genomics, and Biotechnology for Human Health" Priority within the 6th Framework Programme for Research and Technological

Development of the European Commission (5). The Registry was publicly launched in January 2008 in Berlin, has an envisaged duration of 3 years and is planned to be continually developed (5). Ten EU countries – Belgium, the Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Spain, Sweden and the United Kingdom, as well as some non-EU countries Israel, Switzerland, Turkey and the US are involved in the registry (50).

Mission. The mission of the Registry is to:

1. **Provide comprehensive information** on the current status of human embryonic stem cell research in Europe (including information on existing human embryonic stem cell lines, their derivation, molecular characteristics, use and quality) for the public at large as well as legislators and regulators (5, 51);
2. **Act as a platform for coordination and cooperation** (5);
3. **Increase transparency of human stem cell research** by providing links to other repositories, cell banks, regulatory bodies and specific research projects (51);
4. **Standardise human stem cell research** by ensuring comparable quality standards and promoting validation of research findings (5, 51);
5. **Promote the efficient use of existing stem cell lines** (5) and avoid unnecessary creation of new ones (50).

Objectives. The Registry is intended to achieve the following objectives;

1. Define and implement eligibility criteria for listing of human embryonic stem cells in the registry;
2. Establish a working mechanism for registry performance whereby input from existing registries, banks, networks and research initiatives will be incorporated;
3. Establish and disseminate registry criteria as well as the registration, access and quality control mechanisms to human embryonic stem cell providers and users;
4. Develop the technical frame of the registry and to design and implement an Internet-based access mode for cell lines listed in the registry;
5. Develop the registry into a knowledge-service tool of registered human embryonic stem cells for research and application;
6. Provide regular dissemination, communication and updating mechanisms of the registry content (5).

Accessibility. The registry is freely accessible to the research community, governmental bodies, regulators and the public at large and covers more than 175 human embryonic stem cell lines that have been derived in Europe and beyond (5). Providers of these lines as well as researchers who work with them are invited to register free of charge and provide detailed characteristics on their cell lines or information on their research (5).

Management. The Registry is jointly operated by:

1. The Centre of Regenerative Medicine in Barcelona, Spain (5) and
2. The Berlin-Brandenburg Centre for Regenerative Therapies in Berlin (52).

A Scientific Advisory Board of specialists from the field defines, implements and monitors eligibility criteria for the listing of human embryonic stem cell lines in order to guarantee the highest quality of the information provided (5). There is also a Steering Committee, which forms the links between the local human embryonic stem cell research communities in the participating countries and the registry, and provide updated information to the registry on scientific progress and on new cell lines (5).

7.2. Other Stem Cell Registries also including Europe

The Global Stem Cell Registry at the International Stem Cell Forum (53) is a global stem cell registry of data on approximately 60 human embryonic stem cell lines contributed by 20 laboratories (54), set up to record details of stem cell lines and available online for quick, convenient reference by the international scientific community (54). It has the objective to characterize as many human embryonic stem cell isolates as possible (54).

The International Stem Cell Forum was founded in January 2003 to develop a set of agreed global criteria for the derivation, characterization and maintenance of human stem cell lines, to promote global good

practice and to encourage international collaboration and funding support for stem cell research, thus accelerating progress in this research area (55). To achieve these goals, the Forum has invited research groups worldwide to submit stem cell lines from their laboratories for inclusion in a large-scale characterization project (55).

The International Stem Cell Forum runs the International Stem Cell Initiative Project, aiming to establish international set of standards for the characterization of human embryonic stem cells (55). As the registry will contain the data generated by the characterisation project, it will be launched when the project is nearer completion (55).

The International Society for Stem Cell Research also aims to establish a registry for information on the provenance of embryonic stem cell lines and hopes to coordinate with the European Registry for Human Embryonic Stem Cells so that these databases are complementary and interlinked (51).

8. Conclusions

The legal climate in Europe is slightly changing regarding embryonic stem cell research, with more countries permitting research on human embryos under certain conditions. Such a change may favourably influence the appearance of more stem cell repositories, containing embryonic stem cell lines, in a greater number of countries. However, the landscape of stem cell research in Europe still remains fragmented, and the European Registry for Human Embryonic Stem Cells adds an important global resource to the advancement of this research (51). It has even been suggested that, rather than working toward centralized stem cell repositories, efforts should focus on the creation of a centralized registries (4).

Centralized banking of human stem cells is a task that can benefit stem cell researchers and enhance international collaboration but is complicated because the science is rapidly advancing in an environment of heterogeneous laws, guidelines, and ethical standards (4). Therefore harmonization of practices between distributors to establish cohesive standards and aid the global movement of stem cell lines to the research community is needed, since a number of laboratories worldwide provide stem cell lines to the scientific community (7). Harmonization of international guidelines is also necessary to ensure that new developments and therapies, when and if they arrive in the area of regenerative medicine, are acceptable for clinical use (13).

It is also important that each individual tissue bank, operating on an international basis, is established with reference to the applicable national regulatory requirements (13), but at the same time ensures compliance with different regulatory systems, as cross-border exchanges of donor tissues is likely to be a normal feature of new stem cell-based therapies (13). To achieve this goal, harmonization of national regulations of different countries involved in stem cell banking will need to be performed, which in itself is a difficult and time-consuming task.

Provided that the difficulties with harmonization will be overcome, the creation of stem cell banks could help to achieve the following practical objectives:

1. Reduction of the need for individual research teams to generate their own stem cell lines and the number of tissues and embryos used for the projects;
2. Standardization in the characterization of human embryonic stem cells across different human embryonic stem cell lines and different laboratories;
3. Standardization regarding stem cell derivation and culture (1).

Stem cell banking could also help to meet the following ethical imperatives:

1. Ensuring that there is as little unmet need as possible across groups that might benefit from stem cell-based therapies by ensuring the availability of a greater variety of HLA types;
2. Minimizing or avoiding the use of human embryos by providing researchers with access to already banked embryonic stem cell lines;
3. Minimizing the risk of transmitting disease between cell sources and recipients by ensuring rigorous safety tests and quality control (56).

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References:

1. Nieto A, Cobo F, Barroso-delJesús A, Barnie AH, Catalina P, Cabrera CM et al. Embryonic Stem Cell Bank: A Work Proposal. Stem Cell Reviews 2006; 2:117-126.
2. Healy L, Hunt C, Young L, Stacey G. The UK Stem Cell Bank: Its role as a public research resource centre providing access to well-characterised seed stocks of human stem cell lines. Advanced Drug Delivery Reviews 2005; 57: 1981-1988.
3. The International Society for Stem Cell Research. Guidelines for the Conduct of Human Embryonic Stem Cell Research, 21 December 2006 [cited 2008 May 9]; Available from: URL: <http://www.isscr.org/guidelines/ISSCRhESCguidelines2006.pdf>
4. O'Rourke PP, Abelman M, Heffernan KG. Centralized Banks for Human Embryonic Stem Cells: A Worthwhile Challenge. Cell Stem Cell 2008; 2: 307-312.
5. The European Human Embryonic Stem Cell Registry official website [cited 2008 May 7]; Available from: URL: <http://www.hescreg.eu>
6. Daley GQ, Richter LA, Auerbach JM, Benvenisty N, Charo RA, Chen G et al. The ISSCR Guidelines for Human Embryonic Stem Cell Research. Science 2007; 315: 603-604.
7. Healy LE, Ludwig TE, Choo A. International Banking: Checks, Deposits, and Withdrawals. Cell Stem Cell 2008; 2: 305-306.
8. Stacey GN. Cell contamination leads to inaccurate data: we must take action now. Nature 2000; 403: 356.
9. Hunt C. The Banking and Cryopreservation of Human Embryonic Stem Cells. Transfusion Medicine and Hemotherapy 2007; 34: 293-304.
10. Skottman H, Stromberg AM, Matilainen E, Inzunza J, Hovatta O, Lahesmaa R. Unique gene expression signature by human embryonic stem cells cultured under serum-free conditions correlates with their enhanced and prolonged growth in an undifferentiated stage. Stem Cells 2006; 24: 151-167.
11. European Commission Enterprise and Industry Directorate-General. The Rules Governing Medicinal Products in the European Union, Volume 4, Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use. Draft Annex 2: Manufacture of Biological Medicinal Products for Human Use. [cited 2008 May 9]; Available from: URL: http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2007/2007_09/gmp_annex_2_consultation_2007_09_03.pdf
12. European Union Directive 2004/23/EC of the European Parliament and the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. [cited 2008 May 14]; Available from: URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:EN:PDF>
13. Cobo F, Stacey GN, Cortés JL, Concha Á. Environmental monitoring in stem cell banks. Applied Microbiology and Biotechnology 2006; 70: 651-662.
14. European Pharmacopoeia. Pharmaceutical Inspection Convention. Pharmaceutical Inspection Cooperation Scheme, PE 009-1, 1 September 2003. Guide to Good Manufacturing Practice for Medicinal Products [cited 2008 May 28]; Available from: URL: http://www.21cfrpart11.com/files/library/reg_guid_docs/pics_guid.pdf
15. European Pharmacopoeia. European Pharmacopoeia section 2.6.1 (Sterility), Maisonneuve SA, Sainte Ruffine 2004 [cited 2008 May 28]; Available from: URL: http://lib.njutcm.edu.cn/yaodian/ep/EP5.0/02_methods_of_analysis/2.6.__biological_tests/2.6.1.%20Sterility.pdf

16. European Pharmacopeia. European Pharmacopoeia section 2.6.7 (Mycoplasma), Maisonneuve SA, Sainte Ruffine 2004 [cited 2008 May 28]; Available from: URL: http://lib.njutcm.edu.cn/yaodian/ep/EP5.0/02_methods_of_analysis/2.6.__biological_tests/2.6.1.%20Sterility.pdf
17. Cobo F, Stacey GN, Hunt C, Cabrera C, Nieto A, Montes R et al. Microbiological control in stem cell banks: approaches to standardisation. *Applied Microbiology and Biotechnology* 2005; 68: 456 - 466.
18. Directive 2004/C 24/03. Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA 410/01 Rev 2nd October 2003) adopted by the Committee for Proprietary Medicinal Products (CPMP) and by the Committee for Veterinary Medicinal products (CVMP). [cited 2008 May 14]; Available from: URL: <http://www.emea.europa.eu/pdfs/human/bwp/TSE%20NFG%20410-rev2.pdf>
19. The European Agency for the Evaluation of Medicinal Products. Human Medicines Evaluation Unit. 24 February 1999. EMEA workshop on application to pharmaceuticals of assays for markers of TSE. London. [cited 2008 May 12]; Available from: URL: <http://www.emea.europa.eu/pdfs/human/bwp/025799en.pdf>
20. European Medicines Evaluation Agency. (1997), ICH Consensus guideline on quality of biotechnology products: viral safety evaluation of biotechnology products derived from cell lines of human or animal origin, publication n CPMP/ICH/295/95, European Medicines Evaluation Agency, Canary Wharf, London. [cited 2008 May 12]; Available from: URL: <http://www.tga.gov.au/docs/pdf/euguide/ich/029595en.pdf>
21. European Union Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data. [cited 2008 May 14]; Available from: URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:31995L0046:EN:HTML>
22. The UK Steering Committee for the Stem Cell Bank and for the Use of Stem Cell Lines. Code of Practice for the Use of Human Stem Cell Lines. [cited 2008 May 26]; Available from: URL: http://www.ukstemcellbank.org.uk/code_of_practice.html
23. Commission Directive 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells [cited 2008 May 26]; Available from: URL: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2006:294:0032:0050:EN:PDF>
24. Commission Directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells [cited 2008 May 26]; Available from: URL: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_038/l_03820060209en00400052.pdf
25. The European Group on Ethics in Science and New Technologies to the European Commission. Recommendations on the ethical review of hESC FP7 research projects. Opinion No 22. 20 June 2007 [cited 2008 May 26]; Available from: URL: http://ec.europa.eu/european_group_ethics/index_en.htm
26. Personal communication with Paula Martinho da Silva on 27 May 2008.
27. The UK Stem Cell Bank official website [cited 2008 May 7]; Available from: URL: www.ukstemcellbank.org.uk
28. The Andalusian Molecular Biology and Regenerative Medicine Centre official website [cited 2008 May 8]; Available from: URL: <http://www.cabimer.es/en>
29. Centre of Regenerative Medicine in Barcelona official website [cited 2008 May 8]; Available from: URL: <http://www.cmrbarcelona.org>

30. Human Tissue Act 2004. [cited 2008 May 26]; Available from: URL: http://www.opsi.gov.uk/ACTS/acts2004/pdf/ukpga_20040030_en.pdfhttp://www.opsi.gov.uk/ACTS/acts2004/ukpga_20040030_en_1
31. Imperial College London. Nicholson P, Henley P. Human Tissue Act: Implications for Researchers. Powerpoint presentation. [cited 2008 May 26]; Available from: URL: www3.imperial.ac.uk/portal/pls/portallive/docs/1/7292264.PPT
32. South Manchester University Hospitals NHS Trust. Maines A. Human Tissue Act: Implications for Research. October 2006. Powerpoint presentation. [cited 2008 May 26]; Available from: URL: www.researchdirector.org.uk/Governance/HTA_Oct06.ppt
33. The UK Human Fertilisation and Embryology Act (1990) UK. [cited 2008 May 7]; Available from: URL: http://www.opsi.gov.uk/Acts/acts1990/Ukpga_19900037_en_1.htm
34. The UK Human Tissue Authority. Human Tissue Act Questions and Answers [cited 2008 May 26]; Available from: URL: http://www.idrn.org/human_tissue_questions.php
35. The UK Human Fertilisation and Embryology (Research Purposes) Regulations 2001. Statutory Instrument 2001 No. 188. [cited 2008 May 26]; Available from: URL: <http://www.opsi.gov.uk/SI/si2001/20010188.htm>
36. The UK Human Fertilisation and Embryology (Quality and Safety) Regulations 2007. S.I. 2007/1522. Dated 24 May 2007. [cited 2008 May 24]; Available from: URL: <http://www.opsi.gov.uk/si/si2007/20071522.htm>
37. The UK Medical Research Council. Good Research Practice [cited 2008 May 28]; Available from: URL: <http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002415>
38. Morgan R, Thomson JA, Brownsword R, Brownsword R, Halliday S, Grubb A et al. A lack of foresight? Jurisdictional uncertainties in the regulatory interface between the HFEA, the UK Stem Cell Bank and beyond. Legal Studies 2007; 27: 511-535.
39. The Spanish Law 45/2003 of 21 November 2003 amending Law No. 35/1988 of 22 November 1988 on assisted reproduction procedures. [cited 2008 May 25]; Available from: URL: <http://www.boe.es/boe/dias/2003-11-22/pdfs/A41458-41463.pdf> (in Spanish) and from <http://www.who.int> by search.
40. The Spanish Crown Decree No. 2132/2004 of 29 October 2004 establishing the requirements and procedures governing requests to carry out research projects involving stem cells obtained from surplus pre-embryos. [cited 2008 May 25]; Available from: URL: <http://www.boe.es/boe/dias/2004-10-30/pdfs/A35905-35907.pdf> (in Spanish) and from <http://www.who.int> by search.
41. The Spanish Order SCO/393/2006 of 8 February 2006 providing for the organization and operation of the National Bank for Cell Lines. [cited 2008 May 25]; Available from: URL: <http://www.boe.es/boe/dias/2006/02/18/pdfs/A06637-06641.pdf> (in Spanish) and from <http://www.who.int> by search.
42. The Spanish Law No. 14/2006 of 26 May 2006 on assisted human reproduction procedures. [cited 2008 May 25]; Available from: URL: <http://www.boe.es/boe/dias/2006/05/27/pdfs/A19947-19956.pdf> (in Spanish) and from <http://www.who.int> by search.
43. The Spanish Law No. 14/2007 of 3 July 2007 on biomedical research. [cited 2008 May 24]; Available from: URL: <http://www.boe.es/boe/dias/2007/07/04/pdfs/A2886-288848.pdf> (in Spanish) and from <http://www.who.int> by search.
44. The UK National Institute for Biological Standards and Control official website [cited 2008 May 7]; Available from: URL: www.nibsc.ac.uk
45. EU Directive 2006/17/EC: Implementing Directive 2004/23/EC of the European Parliament and the Council as regards certain technical requirements for the donation, procurement, and testing of human tissues and cells. [cited 2008 May 15]; Available from: URL: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_038/l_03820060209en00400052.pdf

46. EU Directive 2006/86/EC: Implementing Directive 2004/23/EC of the European Parliament and the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells. [cited 2008 May 15]; Available from: URL: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_294/l_29420061025en00320050.pdf
47. The UK Medical Research Council. Department of Health Guidelines for the UK Tissue Banks [cited 2008 May 7]; Available from: URL: www.mrc.ac.uk
48. The New York Times. Bank for Human Stem Cells Starts Ethics Debate in Spain. By Dale Fuchs. February 15, 2004 [cited 2008 May 8]; Available from: URL: <http://query.nytimes.com>
49. Spain News and Information in English [cited 2008 May 8]; Available from: URL: http://www.typicallyspanish.com/news/publish/article_13869.shtml
50. International News. European Commission Agrees To Create Embryonic Stem Cell Line Registry. 2 April 2007. [cited 2008 May 9]; Available from: URL: http://www.kaisernetwork.org/Daily_reports/rep_index.cfm?DR_ID=43976
51. Registries and banks. Nature cell biology 2008; 10: 111.
52. The German Berlin-Brandenburg Centre for Regenerative Therapies official website [cited 2008 May 8]; Available from: URL: <http://www.b-crt.de>
53. The International Stem Cell Initiative official website. The International Stem Cell Initiative Project of the International Stem Cell Forum [cited 2008 May 7]; Available from: URL: <http://www.stemcellforum.org>
54. The International Stem Cell Initiative. Characterization of human embryonic stem cell lines by the International Stem Cell Initiative (2007). Nature Biotechnology 2007; 25 (7): 803-816.
55. The International Stem Cell Forum official website [cited 2008 May 7]; Available from: URL: <http://www.stemcellforum.org>
56. Giacomini M, Baylis F, Robert J. Banking on it: Public policy and the ethics of stem cell research and development. Social Science and Medicine 2007; 65: 1490-1500.