a lack of knowledge of shipping in dry shippers or dry ice shippers. Where cells are transported in the absence of temperature data-loggers, consideration should be given to the use of chemical or other indicators to provide information on temperature during transportation.

8. Future applications of human pluripotent stem cell lines

8.1 Evaluation of human stem cell lines for production of biological medicines

Apart from cell therapy, stem cells or cell lines derived from stem cells can be envisaged for use as substrates for the production of biological medical products such as recombinant proteins (e.g., growth factors or monoclonal antibodies), vaccines and conditioned media. A ISCBI subgroup including representatives from the pharmaceutical industry, reviewed the requirements for cells used to manufacture such products and provided the following summary.

Guidelines for the testing of diploid cells, continuous cell lines and stem cells for cell seed, MCB, WCB and end of production cells have been provided by Part B of the document, *"WHO Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products"* [3]. In cases where a stem cell line has a finite lifespan (senescence) and a diploid profile, the ISCBI manufacturing sub-group recommended assessment of the basic characteristics of a stem cell line by following the criteria of other accepted diploid cell lines such as MRC-5 for biologics production. In the case of a stem cell line with a continuous cell line profile (unlimited capacity for population doubling), the group considered that the stem cell line can be included in the continuous cell line classification. As stated by WHO, this proposal can be applied to any animal stem cell lines including human stem cell lines.

Depending on the product that is made, the sub-group also proposed reference to the guidelines described in Table 4.

In addition, specific recommendations for the testing of each product type should be tailored to the origin and the derivation process of the stem cell line and to the functions of the product on a case by case basis. The risks related to contaminants from the stem cell line have to be considered in the testing of each product, that is, viruses, retroviruses and other transmissible agents, cellular DNA, cellular proteins (growth-promoting proteins).

8.2 Preparation of pluripotent stem cell lines for use in toxicology assays

The capability of human stem cell lines to create tissue-like cultures *in vitro*, could provide valuable information on the toxicity of medicines and hopefully avoid some of the serious chronic toxic effects of drugs which were not detected by standard assays [103,104]. The principles of Good Cell Culture Practice [64] are directly relevant to the use of the undifferentiated hPSC lines

Table 4. **Documents providing guidelines for manufacture of biologics from stem cells.**

Guidelines	Vaccines	Recombinant proteins	Conditioned media
WHO/ DRAFT/ 4 May 2010: Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (proposed replacement of TRS 878, Annex 1). See reference WHO 2010a	√	√	√
International Conference on Harmonization, Q5D, Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products, 1997. www.ich.org/LOB/media/MEDIA429.pdf	√	√	
International Conference on Harmonization, Q5A, Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin. www.ich.org/LOB/media/MEDIA425.pdf	√ (a)	√	
International Conference on Harmonization, Q5B, Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products. www.ich.org/LOB/media/MEDIA426.pdf	√ (b)	√	
CBER Guidance for Industry, Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention of Infectious Diseases, 2010. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulation	√		

(a) Applies to recombinant subunit vaccines. Inactivated vaccines, all live vaccines containing self-replicating agents, and genetically engineered live vectors are excluded from the scope of this document.
(b) Applies to subunit vaccines only.

used in the development of toxicology assays. As part of the EC funded multi-consortium cluster Seurat-1 [215] consideration has also been given to the kinds of specific quality control measures needed for hPSC lines and their development [105]. A diverse range of differentiation protocols are being used to develop these assays and the establishment of assay control parameters, and possibly reference preparations of toxicants to provide quality control of the differentiated cultures. This will be vital to ensure reproducibility in assay data and will be paramount for the successful utilization of stem cell-based models in toxicology and drug discovery.

9. Acknowledgements

All contributors who have provided comments as part of ISCBI discussions and meetings, and also the regulatory agencies who provided informal feedback during the development of the manuscript. We would also like to thank the International Stem Cell Forum members [205] *who have continued to support the ISCBI activity.*

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211 UK toolkit for stem cell therapy. www.sc-toolkit.ac.uk/home.cfm

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Appendices

Appendix 1

Appendix 1 (a). Compliance and provenance determination.

(1) Embryo provenance determination	Code	Considerations
(a) Independent review and oversight	B	The protocol for obtaining gametes and embryos from living donors should be subject to independent review. Review and approval of the hESC derivation protocol may be required in some jurisdictions, but is not an essential requirement
(b) Voluntary informed consent	B	hESC-specific consent requirements may exist or subsequent users of hESC lines may be required to obtain lines for which comprehensive consent has been obtained. Bank should seek to obtain documentation of consent protocol
(c) Gratuitous donation	B	Banks should receive assurance that donors were not paid for embryos or storage costs
(2) Compliance determination	**Code**	**Considerations**
(a1) Embryo was donated in a jurisdiction with no explicit prohibition on hESC derivation	B	Accepting embryos from jurisdictions where hESC research is restricted may incur legal liability
(a2) Derivation protocol confirms to any unique legal requirements in jurisdiction where hESC derived	B	Jurisdiction may have unique requirements in addition to international standards for research ethics (e.g., embryo research oversight or licensing); Consistent with 1a
(b) Any line derived using IVF for research purposes, parthenogenesis or SCNT is identified	B	The use of hESC lines derived from embryos created for research purposes are prohibited by some jurisdictions and funding bodies
(c) Consent requirement for third-party gamete donors	A	Some donated embryos may have been created using gametes from someone other than the embryo donor; Some jurisdictions require consent from third-party donors
(c1) hESC lines derived from embryos intended for reproductive use where a third-party donor(s) was contracted to provide gametes	A	Bank or entity performing hESC derivation should review donor/recipient contract for any conditions that would restrict research use Policies regarding the use of such embryos or resulting hESC lines are variable. Bank should review egg-sharing contract or exchange policies Certain end-users may not be able to utilize lines derived from embryos for which gamete donors were paid or where egg sharing, exchange or anonymous donation has taken place. Documentation serves to enable end user to perform use eligibility determination
(c2) hESC lines derived from embryos for which gamete donor(s) participated in egg sharing or exchange programs are identified	A	
(c3) hESC lines derived from embryos created with anonymous gamete donation are identified	A	
(d) Donor medical history	A/PU	Requirement for medical history may vary depending on relationship between donor and recipient of embryo for IVF. If embryos are created specifically for research, gamete donor medical history should be obtained

Code Key:

A	*Advisable (recommended?): Level of attainment recommended at this time by the International Stem Cell Banking Initiative.*
B	*Baseline: Minimum level of attainment generally consistent with the current standard of care for clinical grade stem cell lines.*
NR	*Not recommended: This option not recommended at this time. Consideration subject to revision based on new information.*
PU	*Potentially utility if available but not required: In certain circumstances supplemental information: medical records, biological specimens (e.g., blood or urine specimens) or quality control assays may be available or have been performed. Banks are encouraged to retain access to supplemental information. Absent evidence of utility – safety or clinical efficacy – the acquisition of supplemental information should not be required for the development of clinical grade stem cell lines.*

hESC: Human embryonic stem cell; SCNT: Somatic cell nuclear transfer.

Appendix 1 (b). Informed consent and donor disclosures: compliance determination check list.

2.1 Did the informed consent process communicate the following elements?	Yes	No	N/A
That the somatic tissue/cells would be used for the purpose of stem cell research, including the derivation of stem cell line(s).			
That genetic tests may be performed, including whole-genome sequencing.			
That research may be conducted on human transplantation.			
That the research is not intended to provide direct benefit to the donor(s) except in the case of autologous donation.			
That the cell lines might be used in research involving genetic manipulation of the cells.			
That the cell lines might be used in research involving the mixing of human and nonhuman cells in animal models.			
That the research entails both foreseeable risks and benefits.			
That any stem cell lines created may be used and stored indefinitely.			
That any stem cell lines created may be used in future unspecified research projects.			
That the decision whether to donate would not affect future medical care.			
That confidentiality will be maintained.			
That the cells would be coded or anonymized (i.e. irreversibly de-linked).			
That donor recontact may be possible (unless anonymized).			
That the donor was informed concerning the disclosure (or not) of general, individuals and/or incidental findings.			
That the donor was informed of the right of withdrawal provided this is not overridden by complete anonymization.			
That the stem cell lines derived will be deposited in a repository for long-term storage and use.			
That once the cells have been used in research, the donor will have no further control over any use of the cells or derived stem cell lines.			
That the cells may be distributed to researchers and institutions within and beyond Canada.			
That the cell lines may be used for commercial purposes but without financial benefit to the donor.			
That the donor was informed of the researchers' actual or potential conflicts of interests.			

Appendix 2. Compliance determination: specific issues to consider for hESCs

Prior to initiation of hESC derivation protocol or intent to bank a hESC line, the following compliance issues should be considered (see Appendix 1 to 3).

Appendix 2. Compliance determination: specific issues to consider for hESCs.	
Embryo donation/ hESC derivation	Some jurisdictions explicitly prohibit the derivation of hESC from human embryos. It is not uncommon for individuals residing in prohibitive jurisdictions to inquire about research donation to outside research centers or banks. Embryos originating from prohibitive jurisdiction should not be used for the derivation of hESC lines if an explicit prohibition is/was effective at the time of donation.
IVF for research purposes & parthenogenesis	Some national, sub-national jurisdictions or funding organizations impose limits on hESC line eligibility. For example, certain jurisdictions have adopted explicit policies determining which hESC lines may be used in research, including requiring that such lines only be derived from embryos that were created using *in vitro* fertilization for reproductive purposes and were no longer needed for this purpose. This reproductive use requirement prevents the use of IVF to develop hESC lines specifically for clinical application or the use of parthenogenetic lines. Consequently, lines derived from oocytes (parthinodes) or embryos created for non-reproductive use should be identified as such.
Special considerations for third-party gametes	Most established hESC lines have been derived from embryos that were created using *in vitro* fertilization for reproductive purposes and were no longer needed for this purpose. Gametes used in the creation of reproductive embryos frequently come from intimate partners. There are, however, a proportion of embryos created with gametes from third-party donors. The conditions surrounding the procurement of third-party gametes may influence the compliance determination and should be documented to the extent feasible. Potential factors to consider include the following: • Paid gamete donation: oocyte and sperm donors are routinely financially compensated. Some policies limit the use of hESC lines derived from embryos for which gamete donors were paid [4]. Banks should be aware of any payment or financial compensation restrictions in their jurisdiction. In addition, it should be noted that certain funding organizations have restrictions on the use of hESC lines derived from embryos where gamete donors were financially compensate beyond the reimbursement of expenses. • Use restrictions: it is also advisable to review the donor contract to support provenance determination and ensure there is no clause in the contract that the resulting embryos be used exclusively by the couple to which they were donated or otherwise restricting research use. • Oocyte sharing/exchange programs: various mechanisms exist for the financing of fertility treatment. One mechanism is 'egg sharing' where fertility treatment costs are reduced for the donor who consents to donating a portion of her oocytes to other women seeking treatment for infertility. Jurisdictional variations exist in the interpretation of this kind of arrangement as a financial incentive, compensation or payment. It is important to note that the applicability of the above factors relating to third-party gametes will vary by national, local or supra-national jurisdictions. For instance, all embryos created using *in vitro* fertilization for reproductive purposes and no longer needed for this purpose are potentially eligible in some jurisdictions regardless of third-party donor payment or exchange. However, in other jurisdictions hESC lines derived from embryos for which a gamete donor(s) were paid are not eligible for research or funding. Documentation of the factors above by the banking entity will enable end users to determine if specific lines are eligible for use in their jurisdiction, but such documentation should not be viewed as essential prerequisite for banking.

Appendix 3. Donor screening protocols for assisted reproductive treatments

The majority of existing hESC lines have been derived from embryos intended for assisted reproductive treatments (ART). Cells differentiated from hESC lines have been utilized in clinical trials after extensive safety evaluation by national regulatory bodies. These evaluations incorporate the donors' medical history and tests that are required in the context of ART treatments for screening low-risk donors of gametes. Consequently, there is no evidence at this time to support the need for further screening of donors of embryos used to derive clinical grade hESC lines [8].

Screening assays occurring prior to hESC derivation should be documented. It is sufficient to verify testing was performed in accordance with prescribed regulatory requirements. For instance, gamete donation (from non-intimate partners) is generally regulated as a biological product and, therefore, subject to both donor infectious disease testing and sample screening (21 CFR part 1271, subpart C, 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). Verifying tests performed (as opposed obtaining quantitative results) is sufficient. Testing and screening regulations have evolved over time, so the bank should seek to document the specific screening requirements in place at time of gamete donation.

ART embryos created with anonymous gametes donors should be acceptable for clinical use provided that first, the donor contract is sufficient to support provenance determination (see section 1 Governance and Ethics); and second, gametes and/or gamete donor were subject to any required screening and testing for relevant communicable disease agents and diseases (see section 3.3).

3. hESC lines: additional donor screening and medical records.	
Third-party (allogeneic) donation from ART	In the case of gamete donation for the purpose of embryo creation, medical history requirements may vary depending on the relationship between the donors and the individuals undergoing ART treatment as well as jurisdictional policy. A third-party gamete donor would typically undergo medical screening and a medical history will be obtained. Entities deriving hESC lines have demonstrated the ability to obtain third-party medical history information (www.cirm.ca.gov/CIRMCellLines). Researchers deriving new hESC lines should inquire about the availability of medical history information. Due to privacy and contractual considerations it is generally not possible to re-contact third-party donors. Again, it should be noted that donor-screening requirements have evolved over time, so it is critical to document the time when gamete donation occurred.
Self (autologous) donation from ART	Embryos created from the gametes of sexually intimate partners for self-reproductive use are not necessarily subject to the same screening requirements as third-party (allogeneic) donation. Resulting ART embryos are generally regulated in a manner consistent with requirements for autologous human transplantation. In this case, the individual(s) donating the embryo(s) for hESC derivation are the gamete donors. A medical history is generally performed in the context of ART treatment and may be available. A medical screening and history may also be obtained at time of embryo donation with donor consent. There is evidence from hESC derivation protocols that donors may consent to (1) being re-contacted in the future or (2) allow linkage to their medical records [8]. Consequently, entities deriving or banking clinical grade lines should examine the possibility of donor re-contact and record linkage options when possible.
Gamete donation for research purposes	Blastocysts may also be made specifically for research using assisted reproductive technologies. In this case, it is recommended to obtain a medical history at the time of gamete donation to inform risk assessment. When available, banks should associate anonymous medical history with the banked hESC lines. Banks may also seek to determine whether the donor(s) of gametes used to derive the hESC line underwent a previous medical screening or history consistent with requirements for tissue intended for allogeneic human transplantation. The nature and extent of such screening should be documented.

Appendix 4. Donor selection, eligibility, release criteria and screening procedures: normative and institutional documents

Appendix 4.	
CANADA	Standard Z.900.1 "Cells, Tissues and Organs for Transplantation: General requirements". Canadian Standards Association. (2nd edition under review) Safety of Human Cells, Tissues and Organs for Transplantation Regulations (SOR/2007–118) (Enabling Statute is the Food and Drug Act) http://www.laws.justice.gc.ca/en/SOR-2007–118/FullText.html Guidance Document for Cell, Tissue and Organ Establishments (Safety of Human Cells, Tissues and Organs for Transplantation- April 6th, 2009) http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/cell/cto_gd_ld-eng.pdf Transplantation Registration Application Form http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/frm_0171-eng.pdf Annex E (normative) Exclusionary Criteria for Risk Factors Associated with HIV, HBV, and HCV http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/brgtherap/cto-reg-annexe-eng.pdf Regulations Amending the Food and Drug Regulations (1024—Clinical Trials) (Division 5: Drugs for Clinical Trials Involving Human Subjects) http://www.hc-sc.gc.ca/dhp-mps/compli-conform/clini-pract-prat/reg/1024-eng.php Canadian Institute for Health Research Updated Guidelines for Human Pluripotent Stem Cell Research 2010.
FRANCE	Bioethics Law (2004) Arrêté du 21 décembre 2005 pris en application des articles R. 1211–14, R. 1211–15, R. 1211–16 et R. 1211–21 du code de la santé publique http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000456466&dateTexte= Décret n° 2005–1618 du 21 décembre 2005 relatif aux règles de sécurité sanitaire portant sur le prélèvement et l'utilisation des éléments et produits du corps humain et modifiant le code de la santé publique (partie réglementaire) http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000000636261&dateTexte= Arrêté du 11 avril 2008 relatif aux règles de bonnes pratiques cliniques et biologiques d'assistance médicale à la procréation http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000018829426&dateTexte= Décret n° 2008–588 du 19 juin 2008 transposant en matière de don de gamètes et d'assistance médicale à la procréation la directive 2004/23/CE du Parlement européen et du Conseil du 31 mars 2004 http://www.legifrance.gouv.fr/affichTexte.do?cidTexte=JORFTEXT000019060568&dateTexte=
UNITED STATES	Guidance for Industry. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm091345.pdf International Compilation of Human Research Standards (2012) http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html
SINGAPORE	Guidelines for Healthcare Institutions Providing Tissue Banking: Regulation 4 of the Private Hospitals and Medical Clinics Regulation http://www.moh.gov.sg/mohcorp/uploadedFiles/Publications/Guidelines/institutions_providing_tissue_banking_guidelines.pdf Medicines Act (Chapter 176, ss. 18 and 74) Medicines (Clinical Trials) Regulations http://www.hsa.gov.sg/publish/etc/medialib/hsa_library/health_products_regulation/legislation/medicines_act.Par.41439.File.dat/MEDICINES%20(CLINICAL%20TRIALS)%20REGULATIONS.pdf Medical (Therapy, Education and Research) Act http://statutes.agc.gov.sg/non_version/cgi-bin/cgi_retrieve.pl?actno=REVED-175&doctitle=MEDICAL%20%28THERAPY%2c%20EDUCATION%20AND%20RESEARCH%29%20ACT%0a&date=latest&method=part Human Organ Transplant Act http://statutes.agc.gov.sg/non_version/cgi-bin/cgi_retrieve.pl?actno=REVED-131A&doctitle=HUMAN%20ORGAN%20TRANSPLANT%20ACT%0a&date=latest&method=part&sl=1

Appendix 4.	
SPAIN	Real Decreto 1301/2006 (10 Noviembre, 2006) por el que se establecen las normas de calidad y seguridad para la donación, la obtención, la evaluación, el procesamiento, la preservación, el almacenamiento y la distribución de células y tejidos humanos y se aprueban las normas de coordinación y funcionamiento para su uso en humanos. Ley 14/2006 (26 Mayo, 2006) sobre técnicas de reproducción humana asistida. Real Decreto 65/2006 (30 Mayo, 2006) por el que se establecen requisitos para la importación y exportación de muestras biológicas. Plan Nacional de Sangre de Cordón Umbilical. http://www.ont.es/infesp/DocumentosDeConsenso/plannscu.pdf Programa de Garantía de Calidad en el proceso de donación. Organización Nacional de Transplantes. http://www.ont.es/infesp/Paginas/ProgramadeGarantiadeCalidad.aspx Real Decreto 2132/2004 begin_of_the_skype_highlightingend_of_the_skype_highlighting, de 29 de octubre, por el que se establecen los requisitos y procedimientos para solicitar el desarrollo de proyectos de investigación con células troncales obtenidas de preembriones sobrantes (BOE 30 octubre). Ley 14/2007, de 3 de julio, de Investigación biomédica. ORDEN SCO/393/2006, de 8 de febrero, por la que se establece la organización y funcionamiento del Banco Nacional de Líneas Celulares. Banco Nacional de Líneas Celulares requisitos para depósito y acceso http://www.isciii.es/htdocs/terapia/terapia_bancocelular.jsp Requisitos que debe cumplir la Hoja de Información a los Participantes y el Consentimiento Informado para investigaciones que impliquen la generación de células pluripotentes inducidas (iPS) http://www.isciii.es/htdocs/terapia/terapia_comiteetica.jsp Real Decreto 1527/2010 (noviembre, 2010) por el que se regulan la Comisión de Garantías para la Donación y Utilización de Células y Tejidos Humanos y el Registro de Proyectos de Investigación http://www.boe.es/boe/dias/2010/12/04/pdfs/BOE-A-2010–18654.pdf
INDIA	Guidelines for Stem Cell Research and Therapy. Department of Biotechnology and Indian Council for Medical Research (2013) The Assisted Reproductive Technologies (Draft Regulation), Rules – 2010. Ministry of Health and Family Welfare, Government of India. The Assisted Reproductive Technologies (Draft) Bill. Ministry of Health and Family Welfare, Government of India
AUSTRALIA	Therapeutic Goods (Charges) Amendment Act 2010 (No. 53, 2010). An Act to amend the Therapeutic Goods (Charges) Act 1989, and for related purposes. Australian code of good manufacturing practice for human blood and blood components, human tissues and human cellular therapy products (2013) National Statement on Ethical Conduct in Human Research (2007), developed jointly by National Health and Medical Research Council, Australian Research Council and Australia Vice-Chancellors' Committee Ethical Guidelines on the use of assisted reproductive technology in clinical practice and research (June, 2007), National Health and Medical Research Council. NHMRC Embryo Research Licensing Committee, Information Kit, National Health and Medical Research Council (2008).
UNITED KINGDOM	UKSC Bank, MRC, Code of Practice for the use of Human Stem Cell Lines (April, 2010) **HFEA Code of Practice (8th edition), HFEA (2009)** The Human Fertilisation and Embryology Act (2008) UK Stem Cell Tool Kit http://www.sc-toolkit.ac.uk/home.cfm Data and Tissues Tool Kit http://www.dt-toolkit.ac.uk/home.cfm HTA Code of Practice on Research (2009) Human Tissue Act (2004) Human Tissue (Quality and Safety for Human Application) Regulations 2007 British Standards Institute (BSI) Publicly Available Specification PAS 83:2012 Developing human cells for clinical applications in the European Union and the United States of America. Guide BSI Publicly Available Specification PAS 84:2012 Cell therapy and regenerative medicine. Glossary BSI Publicly Available Specification PAS 93:2011. Characterization of human cells for clinical applications. Guide

Appendix 4.	
SWEDEN	Tissue Law: Lag (2008:286) om kvalitets- och säkerhetsnormer vid hantering av mänskliga vävnader och celler, som reglerar hanteringen av vävnader och celler som ska användas för transplantation, assisterad befruktning och tillverkning av läkemedel. Lagens bestämmelser konkretiseras ytterligare i de föreskrifter som tagits fram av Socialstyrelsen respektive Läkemedelsverket.ocialstyrelsens föreskrifterom donation och tillvaratagande av vävnaderoch celler; beslutade den 18 november 2008.
SWITZERLAND	Federal Act of 19 December 2003 on Research Involving Embryonic Stem Cells (Stem Cell Research Act, StRA) (RS 810.3, Loi relative à la Recherche sur les Cellules Souches (LRCS)), http://www.admin.ch/ch/e/rs/c810_31.html Federal Act of 18 December 1998 on Medically Assisted Reproduction (Reproductive Medicine Act, RMA) (RS 810.1 Loi fédérale du 18 décembre 1998 sur la procréation médicalement assistée (LPMA) www.admin.ch/ch/f/rs/c810_11.html Federal Act of 8 October 2004 on the Transplantation of Organs, Tissues and Cells (Transplantation Act) The Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA) , in force since 1st January 2002 (www.admin.ch/ch/e/rs/c810_21.html) Federal Office of Public Health (www.bag.admin.ch/index.html?lang=en) Swissmedic (Swiss agency for the authorisation and supervision of therapeutic products): the responsible regulatory authority on behalf of the Federal Office of Public Health (www.swissmedic.ch/index.html?lang=en)
JAPAN	The Act of Pharmaceuticals and Medical Devices MHLW: Ministry of Health, Labor and Welfare (25/11/2014) Revision of former Pharmaceutical Affairs Act. Producing regenerative and cellular therapeutic products in firms The Act on Safety of Regenerative Medicine MHLW (25/11/2014) Providing regenerative medicines within hospitals and clinics. The previous guidelines "The Guideline on clinical research using human stem cells" and "Ethical Guidelines for Clinical Research" were abolished. Guidelines on Ensuring Quality and Safety of Products Derived from Processed Human Cell/Tissue Autologous: MHLW Notification No.0208003 (8/2/2008) Allogeneic: MHLW Notification No.0912006 (12/9/2008) Guidelines on Ensuring the Quality and Safety of Products Derived from Processed Human Stem cells Autologous Somatic Stem Cells: MHLW Notification No.0907–2 (7/9/2012) Allogenic Somatic Stem Cells: MHLW Notification No.0907–3 (7/9/2012) Autologous iPS(-Like) Cells: MHLW Notification No.0907–4 (7/9/2012) Allogenic iPS(-Like) Cells: MHLW Notification No.0907–5 (7/9/2012) Embryonic Stem Cells: MHLW Notification No.0907–6 (7/9/2012) Guidelines on the Derivation of Human Embryonic Stem Cells Guidelines on the Distribution and use of Human Embryonic Stem Cells MEXT : Ministry of Education, Culture, Sports, Science & Technology (25/11/2014) Revision of regulations for clinical use of hES cells
THAILAND	Thai Medical Council Regulation (November, 2009) Thai Food and Drug Administration Regulation (March, 2009) Medica l Council's Medical Practice Act BE2525 (AD 1982) Division of Medical Registration of the Department of Health Service Support's Sanatorium Act BE 2525 (AD 1982)

Appendix 4.

SOUTH KOREA	Bioethics and Safety Act (Jun, 2008) http://www.moleg.go.kr/FileDownload.mo?flSeq=25769 (Article 15) Enforcement Decree of Bioethics and Safety Act (Nov, 2009) http://www.moleg.go.kr/FileDownload.mo?flSeq=31613 Enforcement Rule of Bioethics and Safety Act (Dec, 2009) http://www.moleg.go.kr/FileDownload.mo?flSeq=31607 Pharmaceutical Affairs Act (Apr, 2007) Enforcement Decree of Pharmaceutical Affairs Act (Jun, 2007) A draft of "Regulation of Review and Authorization of Biological Products"(Jul, 2009) law on human tissues (19th March 2010), Ministry of Human Welfare (MHW) Enforcement regulations (Oct 2004), MHW Guidelines for Management of cord blood bank (Act 2005), FDA.
TAIWAN	Regulation of Organ Banks Regulation of Human Biobanks The regulation of prevention of infectious diseases Guidelines of research usage of human biopsy, tissue and fluid Guidelines of research ethics for human embryo and embryonic stem cells.
CHINA	人体器官移植条例Regulations on human organs transplantation (4–6–2007) http://wsj.sh.gov.cn/website/b/28586.shtml 骨组织库管理Standard for human musculoskeletal tissue bank(3–1–2011) 眼库管理Standard for human eye tissue bank(3–1–2011) http://www.moh.gov.cn/publicfiles/business/htmlfiles/mohzcfgs/s7850/201009/48944.htm 脐带血造血干细胞治疗技术管理规范Regulations on therapeutic technology of cord blood stem cells (11–13–2009) http://wsj.sh.gov.cn/website/b/48446.shtml 医疗技术临床应用管理办法Regulations on therapeutic technology for clinics (3–2–2009) http://wsj.sh.gov.cn/website/b/43522.shtml **涉及人的生物医学研究**伦理审查办法Ethical Guidelines on the use of human tissue in research (1–11–2007) http://wsj.sh.gov.cn/website/b/28676.shtml
EU	Commission Directive 2006/86/EC 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. (October, 2006) Commission Directive 2006/17/EC 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. (February, 2006) Directive 2004/23/EC of the European Parliament and of 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. (April, 2004) European Parliament legislative resolution on the Council common position adopting a European Parliament and Council directive on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (10133/3/2003 - C5–0416/2003 - 2002/0128(COD)) (December, 2003)
ISBER	Best Practice for Repositories: Collection, Storage, Retrieval and Distribution of Biological Materials for Research (2012)
FACT	Cellular Therapy Accreditation Manual (5th Edition, 2012)
AHCTA	Position Paper: Towards Global Standard for Donation, Collection, Testing, Processing, Storage and Distribution of Allogeneic HSC and Related Cellular Therapies (2008)
ECVAM	Guidance of Good Cell Culture Practice – A Report of the Second ECVAM Task Force on Good Cell Culture Practice (2005)
NCI – NIH-USA	NCI Best Practice for Biospecimen Resources (2011)
ISSCR	Guidelines for the Clinical Translation of Stem Cells (2008) Guidelines for the Conduct of Human Embryonic Stem Cell Research (2006)
OECD	Guidelines for Human Biobanks and Genetic Research Databases (HBGRDs) (2009) OECD Best Practice Guidelines for Biological Resource Centers (2007)

Appendix 5. Material transfer agreements

A material transfer agreement (MTA) is a contract that governs the transfer of tangible research materials between two organizations (the provider, who is the owner/custodian or the authorized licensee of the material and associated data, and the recipient), thereby defining the contractual rights and obligations with respect to the materials and any derivates.

Important issues to consider when drafting or evaluating an MTA include:

- Ownership of the materials.
- Definition and legal status of original/biological materials, modifications of materials and derivates, progeny;
- Definition of commercial purposes, non-profit organizations, investigator or researcher
- Intellectual property rights;
- Publication rights;
- Royalty fees
- Confidentiality;
- Scope of use and restrictions (e.g., non-commercial/academic vs. commercial research; ethical limitations on types of research to be conducted (e.g., limitations on research aimed at the generation of gametes);
- Use of materials in sponsored research (e.g., industry vs. industry/academic sponsored research);
- Transferability of cell line , cell products or data derived from cell products (e.g., genetic sequencing data);
- Conflicts with existing agreements;
- Compliance with laws and ethical guidelines;
- Processing, cost-recovery and other fees
- Warranties;
- Liability;
- Indemnification.

Model material transfer agreements.	
UK Stem Cell Bank	Clinical/Commercial use http://www.ukstemcellbank.org.uk/cell_lines/eutcd_grade_stem_cell_lines/depositing_eutcd_stem_cell.aspx Research Use http://www.ukstemcellbank.org.uk/legal_agreements.aspx
USA National Institutes of Health (NIH), Center for Regenerative Medicine (CRM)	Master Agreement Regarding Use of the Uniform Biological Material Transfer Agreement http://www.crm.nih.gov/researchTools/uniform_transfer_agreement.asp CRM Induced Pluripotent Stem (iPS) Cell Material Transfer Agreement http://www.crm.nih.gov/researchTools/material_transfer_agreement.asp Public Health Service Biological Materials License Agreement http://www.crm.nih.gov/researchTools/bio_mats_agreement.asp
International Society for Stem Cell Research (ISSCR)	ISSCR Sample Material Transfer Agreement http://www.isscr.org/home/publications/guide-clintrans/sample-material-transfer-agreement
ATCC	General MTA http://www.atcc.org/Documents/Product%20Use%20Policy/Material%20Transfer%20Agreement.aspx Research Use http://www.atcc.org/en/Documents/Product_Use_Policy/Research_Use.aspx Commercial Use http://www.atcc.org/en/Documents/Product_Use_Policy/Commercial_Use.aspx
California Institute for Regenerative Medicine (CIRM)	http://www.cirm.ca.gov/our-funding/stem-cell-regulations-governing-cirm-grants BioTimes hESC Lines http://www.cirm.ca.gov/our-funding/biotime-stem-cell-lines-agreement
WiCell	iPS Wisconsin MTA http://www.wicell.org/media/WiCellAgreements/WiCell-iPS-MTA.pdf UCSF MTA http://www.wicell.org/media/WiCellAgreements/WiCell-UCSF-Material-Agreement.pdf
Wisconsin Alumni Research Foundation (WARF)	Agreements http://www.warf.org/home/for-industry/Agreements/agreements.cmsx

Appendix 6. An example of release criteria*: characterization data for information** and specifications for seed stocks of undifferentiated hPSC lines

Test	Examples of test method(s)	Criteria/specification	Test results prior to release
Identity1 *	Typically Short Tandem Repeat (STR) Testing (other techniques may be used such as, Human Leukocyte Antigen (HLA) Testing	All alleles match parent cell line	Meets Specification
Bacteria/Fungi (sterility) 2*	Inoculation of microbiological media to detect growth of bacteria and fungi2	No detectable contamination	Meets Specification
Mycoplasma2*	Pharmacopeia tests include direct culture, direct stain (DAPI or Hoechst 33258) and Vero culture followed by direct stain. Alternative PCR tests are now becoming acceptable	No detectable contamination (sensitivity and specificity to be validated with service provider)	Meets Specification
Karyotype3*	Chromosome count of 20 metaphases and G-band analysis of a further 10 metaphases (see ISCBI [2009] and Section 4)	Diploid chromosomes predominant in cells analysed (for specifications see section 4).	Meets Specification
Viability2 *	Viability must be quantified using a validated method. A lower limit for acceptability should be indicated	Viability should typically be ≥50% of thawed cells (N.B. this does not necessarily equate with functional performance of the culture and is merely an indicator of the ability to expand cells from production purposes)	Meets Specification
Growth characteristics*	Determine doubling time	Typically 20 to 40 h	Meets Specification
Characterization and stability (N.B. stability testing will need to be established by each repository, but may include culture to passages or population doublings to limits anticipated for cell therapy products) **			
Antigen expression	Flow cytometry of hPSC markers of self renewal and hPSC state (these are to be selected and qualified the repository but possible examples include Oct-4, TRA 1–60, TRA 1–81, SSEA-3, SSEA-4, Alkaline Phosphatase, Rex-1, SSEA-1 negative)	Typically ≥70% of hPSCs expressing hPSC markers and ≤10% of hPSCs expressing SSEA-1 (N.B actual values should be based on local experience with each cell line)	Meets Specification
Pluripotency**	Tests indicating potential pluripotency (e.g., teratoma production, embryoid body formation, directed differentiation - see section 4.6)	Criteria should be set by repository depending on method used, but embryoid bodies and teratomas should express markers of ectoderm, mesoderm and endoderm.	Meets Specification
Viral contamination4*	*In vitro* and *in vivo* non-specific and specific (virus screening should be directed by risk assessment and where there is risk of blood born virus contamination may include viruses such as HIV 1 and 2, HBV, HCMV, HCV, HHV 6–8, EBV, HTLV I&II, B19 etc.)	No detectable contamination (N.B. levels of sensitivity will need to be validated by the repository or service provider)	Meets Specification
Reprogramming factors*	Test to assure silencing of reprogramming vectors or elimination of episomal non-integrating vectors	RTPCR/qPCR, antibody based detection	Reprogramming vectors and or exogenous expression of reprogramming factors not detectable

**Release criteria should include test sensitivity and test specificity where appropriate.*
***Characterization for information not release.*
****Testing should be performed on at least 1% of vials, but no less than 2 of the Bank from which cells are to be released.*
1. Cell line identity must be reflected by the 'product label' for packaging.
2. Suitable tests are described in the European Pharmacopoeia methods and 21 CFR 610.30.
3. For further information, refer to the Consensus Guidance for Banking and Supply Of Human Embryonic Stem Cell Lines For Research Purposes (reference ISCBI (2009) in main text)(1)
4. Suitable tests are described in the ICH guidelines Q5A [106].
5. Cell banks should be free of extraneous material apart from that which is unavoidable in the manufacture process. For further information, refer to ICH Q3 on 'Impurities'[107]
6. It is important to note that the tests indicated here are examples of tests applied typically to pharmaceutical products, and whilst they may add value by detecting contamination that may not be detected in a standard phamacopeial 'sterility' test, they may also miss certain bacterial contaminants lacking the cell wall components detected in pyrogencitiy and limulus lysate assays. These tests may also give false positive results where contamination is not present but bacterial components persist in cell culture reagents. Cell banks should keep a watching brief for alternative qualified tests, which may become available and give broader capacity for detecting both bacterial and fungal contamination such as PCR for microbial ribosomal RNA.

Test	Examples of test method(s)	Criteria/specification	Test results prior to release
Purity [5]			
Differentiated cells*	Flow cytometry using hPSC and non-hESC markers	Contamination with non-hPSC markers should be below levels	Meets Specification
Cell debris**	Flow cytometry (of note, markers and acceptable limit may vary with cell line and local culture procedures)	Maximum levels of cell debris specified based on local data on each cell line.	Meets Specification
Non-specific tests for bacterial contamination	Examples include: a) Endotoxin [7, 8]**: limulus amaebocyte lysate (LAL) test b) Pyrogenicity [8,9] **: Rabbit pyrogen test method c) PCR for microbial rRNA genes:	Acceptable levels will need to be defined and validated locally (international standards to qualify	Meets Specification
Vial labelling**	A water-resistant written, printed or graphic indication must be affixed to each container/ package of hPSCs describing critical information about the cells/product	See section 5.7	Meets Specification

**Release criteria should include test sensitivity and test specificity where appropriate.*
***Characterization for information not release.*
****Testing should be performed on at least 1% of vials, but no less than 2 of the Bank from which cells are to be released.*
1. Cell line identity must be reflected by the 'product label' for packaging.
2. Suitable tests are described in the European Pharmacopoeia methods and 21 CFR 610.30.
3. For further information, refer to the Consensus Guidance for Banking and Supply Of Human Embryonic Stem Cell Lines For Research Purposes (reference ISCBI (2009) in main text)(1)
4. Suitable tests are described in the ICH guidelines Q5A [106].
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Appendix 7. Examples of QA definitions used in GMP manufacture

The terminologies given here are purely examples drawn primarily from the FDA tissue banking regulation [108]. There are no wholly agreed terminologies for this area and it is therefore important to use the definitions of QA terms recommended in national guidelines. In some cases there are significant difference in the scope of a definition under different jurisdictions such as the definitions for serious adverse events in the EU and the USA. ICH definitions [109] is very similar to FDA Medwatch and is probably one of the best harmonized terminologies. The PAS terminology [2] provides the UK and EU definitions and the regulatory reference for QA terms in Europe is the European Tissues and Cells Directive.

QA DEFINITIONS

ACCEPTANCE CRITERIA: The specifications and acceptance/rejection criteria, such as acceptable quality level and unacceptable quality level, with an associated sampling plan, that are necessary for making a decision to accept or reject a lot or batch of raw material, intermediate, packaging material, or product. This term can also be applied to validation.

ADVERSE EVENT: Any untoward medical occurrence in a patient or clinical investigation subject administered with a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

ADVERSE REACTION: A noxious and unintended response to any human cells, tissues, and cellular and tissue-based products for which there is a reasonable possibility that the HCT/P caused the response.

ASEPTIC PROCESSING: The processing of cells/product by methods that avoid or minimize contamination with microorganisms from the environment, processing personnel and/or equipment.

AUDIT: A review of procedures, records, personnel activities, reagents, materials, equipment and facilities to determine adherence to standards and regulations.

BATCH: A batch, sometimes called lot, is defined as an entity, by either time or quantity or both, of a product that is intended to have a uniform character and quality. A batch must be produced within predefined and specified conditions following a defined manufacturing process.

BATCH MANUFACTURING RECORD (BMR): The necessary quality documentation for tracing the complete cycle of manufacture of a batch or lot.

BATCH RECORD REVIEW: The process of reviewing and approving all Product Manufacturing and control records is called the batch record review. This includes, but is not limited to, packaging and labeling. The batch record review is performed by the quality unit to determine compliance with all established approved written procedures before a batch is released.

DISPOSITION: The destination of cells/product for research, transplantation or discard.

DISTRIBUTION: A process including the receipt of a request for, selection of, and inspection of cells/product, and their/its shipment for delivery to recipient.

DOCUMENTATION: Any procedures, instructions, logbooks, records, raw data, manuals, and policies associated with the development, manufacture, testing, marketing and distribution of a product required demonstrating compliance with applicable worldwide regulatory requirements.

EQUIPMENT QUALIFICATION: Protocols to evaluate equipment performance following instillation and before use, to ensure normal function within required tolerance limits.

FACILITIES: The facilities are used for the manufacturing of cell therapy products with predefined environmental control following the applicable standards of e.g., particulate and microbial contamination. The facilities should be constructed and used reducing the introduction, generation and retention of contaminants within the area.

IN-PROCESS CONTROL (IPC): Testing and activities performed during production to monitor and, if necessary, adjust the process to assure that the product conforms to its specifications.

INTERMEDIATE: An intermediate product e.g., cell line that must undergo further processing before it becomes a final product.

LABEL: A written, printed or graphic indication affixed to a container/ package describing critical information about the cells/product.

LOT: Cells/product derived from one donor, banked at one time using the same reagents and materials, and identified by a unique identification number.

PROCEDURE: A series of ordered steps designed to achieve a specific outcome when followed.

PROCESS VALIDATION: Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

QUALITY: The term quality is used as the totality of features and characteristics of a product that bears on its ability to satisfy stated or implied needs including the conformance to requirements to specifications.

QUALITY ASSURANCE: A formal methodology designed to provide adequate confidence that the entire production of a product will fulfil requirements for quality under a wide conditions of operation. Quality assurance includes formal review of care, problem identification, corrective actions to remedy any deficiencies and evaluation of actions taken.

QUALITY ASSURANCE UNIT: Sets policies, procedures and specifications, audits, reviews, assesses and training including continuous evaluation of the adequacy and effectiveness of the overall quality program.

QUALITY CONTROL: A procedure or set of procedures intended to ensure that a manufactured product adheres to a defined set of quality criteria.

QUALITY CONTROL UNIT: The function in the quality unit that is responsible for the ongoing control of product and environment quality. Therefore the quality control unit (QC) has the overall responsibility for acceptance or rejection of e.g., raw materials, cell lines/intermediate products/final products, packaging components.

IN-PROCESS CONTROLS (IPC), LABELLING AND INSPECTION: Assurance that supporting systems are being controlled and monitored.

QUALITY SYSTEM: Organizational structure, responsibilities, procedures, processes, and resources for implementing quality management.

QUARANTINE: The storage of materials/cells/ product in an isolated area until deemed safe (cleared/approved) for use.

SERIOUS ADVERSE EVENT/REACTION (ICH DEFINITION: Topic E2A1): Is an untoward medical occurrence which is: fatal, life-threatening (risk of death at the time of the event), disabling, or incapacitating resulting in hospitalization, or medically significant congenital abnormalities.

SERIOUS ADVERSE EVENT (EU TCD): Any untoward occurrence associated with the procurement, testing, processing, storage and distribution of tissues and cells that might lead to the transmission of a communicable disease, to death or life-threatening, disabling or incapacitating conditions for patients or which might result in, or prolong, hospitalization or morbidity

SERIOUS ADVERSE REACTION (EU TCD): Unintended response, including a communicable disease, in the donor or in the recipient associated with the procurement or human application of tissues and cells that is fatal, life-threatening, disabling, incapacitating or which results in, or prolongs, hospitalization or morbidity.

SPECIFICATIONS: Used for the predefined written, chemical, physical, biological and environmental characteristics for testing a product or system. This includes, but is not limited to, starting materials, packaging materials, intermediate, bulk, or product.

STANDARD: An accepted or authoritatively established principle or practice for quality assurance (e.g., SOP).

STANDARD OPERATING PROCEDURE: A detailed description of a procedure or process for quality assurance.

TRACEABILITY: The ability to locate cells/product at any point/step during production, processing, testing, storage, distribution or disposition.

VALIDATION: The procedure for establishing documented evidence that a specific system is constructed and operates according to a predetermined set of specifications and guidelines. Validation includes but is not limited to: equipment, computer systems, production processes, cleaning procedures, facilities, utilities as well as analytical methods.

Appendix 8: Preservation technologies and methods

Mode of cryopreservation

Two approaches to cryopreservation have been applied to stem cells: vitrification and slow cooling [101]. Both of these are capable of ensuring high survival if appropriately applied.

Vitrification

The vitrification method currently applied is a non-equilibrium approach relying on ultra-rapid cooling with low concentrations of CPA to achieve the ice-free vitreous state. This is a meta-stable state which is prone to de-vitrification (with the potential for subsequent damaging ice formation) if those conditions necessary to maintain the vitreous state (notably a stable low temperature) are not maintained (see storage and transportation).

The choice of container and the unit volume of material being cooled should be considered when vitrification methods are employed, since both these will affect the maximum attainable cooling and warming rate. The ultra-rapid cooling rates necessary to effect vitrification require both high surface to volume ratios (with regard to container geometry) and small volumes (of the order of microliters per unit sample). In preparing large banks of cells, consideration should be given to the practicality of this method for scale-up due to the need to preserve relatively small numbers of cells at one time.

Consideration should also be given to the use of open straws and Dewars containing non-sterile liquid nitrogen (LN_2) into which the straws are plunged. Neither of these can be considered to be best practice both from a microbiological or regulatory perspective. Alternatives to the open straw method, such as closed straws and straw-in-straw methods, should be considered, but there may also be important logistical constraints (e.g., size of the bank, mode of transportation) which must be reconciled with the requirements of the preservation method.

Other alternatives for ice-free preservation, such as equilibrium approaches utilizing high concentrations of CPA [100,110] and/or the addition of natural or synthetic ice blocking molecules coupled with slow cooling [111] have not as yet been applied to stem cells.

Conventional slow cooling

During slow cooling, ice formation will occur within the system resulting in the concentration of solutes in the remaining liquid phase in which the cells reside. Damage results mainly from exposure to these high solute concentrations (so-called solution effects), but may also occur as a result of intracellular ice formation. Ice formation within cells is generally a consequence of rapid cooling, but may occur in tissues at slow cooling rates as a random event leading to ice propagation to surrounding cells. It should be noted that CPAs militate against damaging solution effects of slow cooling but not against damage caused by intracellular ice formation.

Conventional slow cooling methods are generally more amenable to the production of large banks of cells produced as 'single' cell suspensions. For stem cells cryopreserved as colony fragments, if slow cooling methods are to be applied, consideration should be given to methods to control ice nucleation such as the inclusion of ice nucleating agents or seeding samples at high sub-zero temperature [112].

Methods of cooling

The high cooling rates required for vitrification are generally obtained by direct immersion of the sample into a cryogen, usually liquid nitrogen. Slow cooling can be effected by either controlled rate cooling or the use of passive cooling devices. In both cases, consideration must be given to issues of sample contamination and contamination of the cleanroom as well as those of reproducibility and validation (see validation).

Controlled rate freezers (CRFs) in which the chamber containing the product is cooled by the injection of LN_2 will generally be located outside the cleanroom environment unless the resulting nitrogen vapour can be ported to the outside of the cleanroom and the chamber can be effectively sterilized between cooling cycles. If such devices are used, outside the production area, consideration should be given to the method by which cells are moved to the CRF, to ensure that CPA exposure time/temperature does not compromise cell survival or lead to contamination.

Liquid nitrogen-free, CRFs, such as those employing the Stirling Cycle principle, may provide an alternative [113,114]. While such equipment provides a clean room-compatible solution for controlled rate freezing, they should be assessed for their ability to provide the required cooling rates, unit volumes and bank sizes appropriate to the cell lines being banked.

The end point temperature at which cells are transferred from the CRF to low-temperature storage should be set at a sufficiently low temperature to ensure that during handling and transfer to permanent storage any rise in temperature of the samples does not expose the cells to damaging sub-zero temperatures (above approximately -70°C for frozen cells and above the glass transition temperature for vitrified material).

Passive cooling devices are generally placed inside a mechanical freezer to equilibrate. A uniform and reproducible cooling rate can be obtained if there is careful control of the sub-zero environment. A sub-zero temperature of at least -70°C should be employed in order to limit the cells exposure to the most damaging sub-zero temperatures (between the equilibrium freezing point and ~ -40 to 60°C) and assist in providing a relatively linear cooling rate over this temperature range. Consideration should be given to temperature logging of a control sample for QC purposes, the use of a designated freezer and procedures to control access to this freezer during cryopreservation.