

REGULATION OF STEM CELL-BASED PRODUCTS

Barbara von Tigerstrom and Erin Schroh*

As stem cell research moves toward offering more clinical applications, questions arise about how relevant products will be regulated. To date these questions have received relatively little attention compared to the legal and ethical issues associated with stem cell research,¹ but they will become increasingly important as technology advances. In consultations on the pressing ethical issues relevant to stem cell translational research, one of the concerns identified was the “adequacy of our current system of oversight for both innovative therapies and clinical trials for addressing the unique challenges presented by stem cell research.”²

This article will outline and discuss the regulatory regimes that would apply to stem cell-based products as therapeutic products. Part one provides an introduction to stem cells and their potential therapeutic uses, including the different types of stem cell-based products and the safety, efficacy and quality issues associated with these products. Part two then describes the regulatory regimes that would apply to stem cell-based products in Canada, the United States, Europe and Australia. Finally, the third part discusses the key issues and challenges that arise in the regulation of these products.

* Barbara von Tigerstrom, Assistant Professor, College of Law, University of Saskatchewan, Saskatoon. Erin Schroh, University of Saskatchewan LLB 2008. Acknowledgements – The authors would like to acknowledge research assistance by Jodi Roach, Bobbi-Jo Cammer, and Jacqueline Shaw, as well as helpful comments by an anonymous reviewer. This research was funded under a core grant from the Stem Cell Network, “Towards the Clinic?: Ethical, Legal and Social Issues (ELSI) Relevant to Emerging Stem Cell Therapies.”

1 See e.g., Dina Gould Halme & David A. Kessler, “FDA Regulation of Stem-Cell-Based Therapies” (2006) 355 *New Eng. J. Med.* 1730; Kathleen Liddell & Susan Wallace, “Emerging Regulatory Issues for Human Stem Cell Medicine” (2005) 1 *Genomics, Society and Policy* 54; Lincoln Tsang, “Legal and Ethical Status of Stem Cells as Medicinal Products” (2005) 57 *Advanced Drug Delivery Reviews* 1970.

2 Ubaka Ogbogu, “A Review of Pressing Ethical Issues Relevant to Stem Cell Translational Research” (2006) 14:3 *Health Law Review* 39 at 41.

As we will see, the variety of potential stem cell-based products means that they may be classified in different ways. In addition, the jurisdictions surveyed define and classify products differently, although all have generally similar procedures and requirements for approval of therapeutic products. The regulatory frameworks in these jurisdictions have been undergoing reforms to accommodate new types of products, especially human cell- and tissue-based products. However, many products still do not fit comfortably within existing categories. This uncertainty, combined with the differences between jurisdictions, may present a barrier to the development and marketing of stem cell products. In addition, there are a number of challenging safety, efficacy and quality issues relating to these products, and the relationship between product regulation and the legal and ethical issues surrounding the use of stem cells requires further consideration.

1. Stem Cell-Based Products

a. Stem Cells and Their Potential Clinical Applications

Stem cells are unspecialized cells which differentiate into various specialized cell types. They possess two special characteristics which make them uniquely valuable in medical research and, potentially, treatment: they are capable of self-renewal (i.e. they can divide and replicate themselves indefinitely) and of differentiation into one or more specialized cell types.³

There are two main sources of stem cells: human embryos and adult tissue. Embryonic stem cells (ES cells) may be derived from the inner cell mass of early embryos (blastocysts) created by fertilization or by the transfer of a somatic cell nucleus into an unfertilized, enucleated human egg (nuclear transfer). ES cells are pluripotent, meaning they are able to dif-

3 Abdallah.S. Daar & Lorraine Sheremeta, "The Science of Stem Cells: Some Implications for Law and Policy" (2002) 11:1 Health Law Review 5 at 5; R.A. Musina, Ye.Ye. Yegorov & A.V. Belyavsky, "Stem Cells: Properties and Prospective Medical Applications" (2004) 38 Molecular Biology 469 at 469. There has been some recent debate regarding this definition of stem cells, since it has been observed that mature cells may also have a limited ability to de-differentiate or trans-differentiate: Julia M. Polak & Anne E. Bishop, "Stem Cells and Tissue Engineering: Past, Present, and Future" (2006) 1068 Annals of the New York Academy of Sciences 352 at 354.

ferentiate into cells of any of the three germ layers (ectoderm, mesoderm, and endoderm). Adult stem cells may be derived from umbilical cord blood, spinal fluid (amniotic fluid-derived) or adult organs and tissues. Their plasticity (ability to differentiate into different cell types) is more limited than ES cells, and they generally differentiate into cells of a particular type. However, it is now believed that adult stem cells have some capacity to trans-differentiate (differentiate into cells of other types).⁴ Adult stem cells may be categorized based on the types of cells into which they differentiate. Hematopoietic stem cells develop into various types of blood cells. Mesenchymal stem cells may develop into cartilage, bone, fat and marrow. Neural stem cells differentiate into brain cells, commonly nerve cells, astrocytes and oligodendrocytes.

Therapeutic uses of stem cells can be distinguished according to the relationship between the source and recipient of the cells. In an allogeneic transplant, the donor and the recipient are separate individuals; the donor and recipient may be related or unrelated. In an autologous transplant, the recipient's own cells are used. A xenographic transplant utilizes cells from a non-human animal. In any of these, stem cells may be transplanted for homologous use, such that they perform their original function, or non-homologous use, in which the cells perform a different function.

One of the challenges in discussing the regulation of stem cell-based products is the diverse array of such products that are currently being investigated and developed.⁵ Anna W. Wobus and Kenneth R. Boheler identify four therapeutic concepts for the use of stem cells: direct administration, transplantation of differentiated stem cell progeny, tissue engineering, and induced self-repair.⁶ These categorizations provide an appropriate context for understanding the issues concerning the regulation of stem cell-based products.

4 Daar & Sheremeta, *ibid.* at 6.

5 For a sample of companies engaged in product development and their products, see Ken Howard Wilan, Christopher Thomas Scott & Stephan Herrera, "Chasing a Cellular Fountain of Youth" (2005) 23 *Nature Biotechnology* 807, tables 1 and 3.

6 Anna M. Wobus & Kenneth R. Boheler, "Embryonic Stem Cells: Prospects for Developmental Biology and Cell Therapy" (2005) 85 *Physiological Reviews* 635 at 666-67. See also Musina, Yegorov & Belyavsky, *supra* note 3 at 475.

In direct administration, stem cells are introduced locally or systemically into the patient's body.⁷ The cells then migrate to the intended site and differentiate into the appropriate cell type.⁸ ES cells can only be used in this process under certain conditions to avoid the risk of tumour formation.⁹ This method may be used for such treatments as cardiovascular and liver repair.¹⁰ A variation of this process utilizes stem cells as vectors to deliver therapeutic agents. This method may be used in cancer treatment, for example, exploiting the tendency of some stem cells to migrate to tumour sites.¹¹

Transplantation of differentiated stem cell progeny refers to techniques in which stem cells are cultivated *in vitro*, differentiated into the desired tissue type and then transplanted into the desired site.¹² An advantage of this approach is that purified cell progeny can be isolated and transplanted.¹³ It is envisioned this method will be available for treatment of diabetes, such that cellular grafts will normalize blood glucose levels with insulin-secreting cells.¹⁴ This method may also provide treatment for stroke¹⁵, Parkinson's disease,¹⁶

7 Wobus & Boheler, *ibid.* at 666.

8 *Ibid.*

9 *Ibid.*

10 In the context of cardiovascular treatment, see Charles E. Murry, Hans Reinecke & Lil M. Pabon, "Regeneration Gaps: Observations on Stem Cells and Cardiac Repair" (2006) 47 *Journal of the American College of Cardiology* 1777; Charles A. Goldthwaite, "Mending a Broken Heart: Stem Cells and Cardiac Repair" in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington, D.C.: National Institutes of Health, 2006) 57, online: <<http://stemcells.nih.gov/info/scireport/2006report.htm>>; Wobus & Boheler, *ibid.* at 663. In the context of liver repair, see: Andy Coghlan, "Bone Marrow Stem Cells Prop Up Failing Livers" *New Scientist Magazine* 188:2520 (8 October 2005) 13.

11 Riccardo Fodde, "Stem Cells and Metastatic Cancer: Fatal Attraction?" (2006) 3:12 *PLoS Medicine* 2182.

12 Wobus & Boheler, *supra* note 6 at 667.

13 *Ibid.*

14 *Ibid.*

15 Olle Lindvall & Zaal Kokaia, "Stem Cells for the Treatment of Neurological Disorders" *Nature* 441:7097 (29 June 2006) 1094 at 1095.

16 *Ibid.*; Tracy Hampton, "Stem Cells Ease Parkinson Symptoms in Monkeys" (2007) 298 *Journal of the American Medical Association* 165 at 165; David Panchision, "Repairing the Nervous System with Stem Cells" in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington: D.C.: National

and other neurological diseases,¹⁷ although evidence of proper re-integration has not yet occurred in this context.¹⁸

Stem cells are also used in tissue engineering to construct three dimensional structures which are then inserted and integrated into the relevant site. Tissue engineering generally refers to “the design and construction in the laboratory of living, functional components that can be used for the maintenance, regeneration, or replacement of malfunctioning tissues.”¹⁹ Engineered tissues are typically composed of cells seeded onto a scaffold or matrix, where they form into the required tissue.²⁰ Stem cells are being explored for use in tissue engineering because they have the potential to overcome some of the limitations of using primary cells.²¹ Examples include engineered skin, bone, cartilage, and blood vessels.²²

In induced self-repair, the patient is injected with growth factors in order to stimulate existing stem cells;²³ no transplant is required. While bone marrow is the only source currently usable by this process,²⁴ other possible stem cell sources include the liver, brain, skin, heart and intestine.²⁵

Finally, in addition to these direct clinical applications, stem cells may also be used in testing new pharmaceuticals or treatments for disease. Stem cells are being developed and marketed as disease models and testing screens to be used in preclinical testing in addition to or in the place of animal test-

Institutes of Health, 2006) 35 at 39-40, online: <<http://stemcells.hih.gov/info/scireport/2006report.htm>>.

17 Including Huntington’s disease, amyotrophic lateral sclerosis, Alzheimer’s disease, multiple sclerosis and spinal cord lesions. See e.g. Panchision, *ibid.* at 40-41. While some of these treatments may be realized through direct administration, it is suggested that the most effective procedure would involve some type of genetic modification: Lindvall & Kokaia, *supra* note 15 at 1095.

18 Lindvall & Kokaia, *ibid.* at 1094.

19 Polak & Bishop, *supra* note 3 at 352.

20 *Ibid.* at 353; Wobus & Boheler, *supra* note 6 at 667.

21 Polak & Bishop, *ibid.* at 354; Meredith Lloyd-Evans, “Regulating Tissue Engineering” (2004) 7:5 *Materials Today* 48 at 49.

22 Polak & Bishop, *ibid.* at 361; David Williams, “Benefit and Risk in Tissue Engineering” (2004) 7:5 *Materials Today* 24 at 25; Wobus & Boheler, *supra* note 6 at 667.

23 Wobus & Boheler, *ibid.*

24 *Ibid.*; H.J. Rippon & A.E. Bishop, “Embryonic Stem Cells” (2004) 37 *Cell Proliferation* 23 at 24.

25 See e.g. Panchision, *supra* note 16 at 40.

ing.²⁶ These do not contemplate direct clinical uses of stem cells but rather making use of them in the development of other clinical products.

In these various types of applications, there is the possibility of genetically manipulating stem cells for specific purposes. This would not be a separate therapeutic concept in itself but rather an approach that could be applied in one of the therapeutic concepts described above. Stem cells, especially ES cells, are "amenable to genetic manipulation," which "offers the possibility to introduce genes to promote lineage-restricted differentiation and provides the basis for gene therapy to introduce therapeutic genes and potentially to modulate the immune response allowing implantation of 'non-self' cells/tissues."²⁷ Adult or embryonic stem cells may be used in several forms of gene therapy.²⁸ Using stem cells as primary recipients of recombinant DNA in gene therapy may be safer and more effective than direct administration of DNA to humans.²⁹ The products resulting from these techniques would be stem cell-based products but also fall within the definition of gene therapy.

While these various uses of stem cells potentially raise some common issues, for example with respect to concerns about the use of ES cells on ethical or religious grounds or the donation of gametes and embryos, in the context of therapeutic product regulation they also raise quite distinct issues. The scope of stem cell-based products for the purposes of the discussion below will therefore be somewhat narrower than the range just surveyed. As used in this article, the term "stem cell-based product" refers to a product intended to be administered to a patient that contains stem cells or is derived from stem cells (i.e. contains stem cell progeny). Of the therapeutic concepts just surveyed, this would therefore include direct administration, transplantation of differentiated stem cell progeny, and tissue engineering. Not included is induced self-repair, which does not contemplate any direct manipulation or administration of stem cells outside the human body but rather the administration of substances to induce a particular physiological effect (similar to other pharmaceutical products). The use of stem cells as disease models and in preclinical drug testing will also be excluded from the

26 Wilan, Scott & Herrera, *supra* note 5 at 811.

27 Polak & Bishop, *supra* note 3 at 359.

28 Thomas P. Zwaka, "Use of Genetically Modified Stem Cells in Experimental Gene Therapies" in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington, D.C.: National Institutes of Health, 2006) 45 at 45-52, online: <<http://stemcells.nih.gov/info/scireport/2006report.htm>>.

29 Musina, Yegorov & Belyavsky, *supra* note 3 at 476.

scope of products discussed below, since these do not fall within common definitions of therapeutic products. This grouping of products is consistent with other comparable analyses,³⁰ and with evolving regulatory approaches, as will be seen below.

b. Safety, Efficacy and Quality Issues in Stem Cell-Based Products

The main objective of regulatory regimes for therapeutic products is to ensure that these products are safe, effective, and of high quality, in order to protect the health and safety of prospective consumers or patients. Any therapeutic product carries risks that need to be weighed against its potential benefits. Because of their characteristics and the emerging state of the technology, stem cell-based products raise a range of safety, efficacy and quality issues that may be challenging for regulatory regimes to address.

Biological products (that is, therapeutic products that are derived from living material) generally present greater challenges in terms of ensuring safety, efficacy and quality compared to pharmaceutical drugs in several respects. These products are more sensitive to even slight changes in production. It has been estimated that over 2000 product quality tests are required for biologicals, compared to less than 100 such tests for small molecule drugs.³¹ In addition, the "biological and chemical properties of biologics cannot at present be predicted fully by physico-chemical means."³² Finally, most biological products will provoke some immune reaction.³³ There are also greater questions about the extrapolation of results of safety, efficacy and quality tests from a reference product to biosimilar products.³⁴

In addition to these challenges, which are common to all biological products, stem cell-based products raise a number of specific issues. As the development and implementation of stem cell technology is a potentially long and complex process, risks arise at each stage, which may threaten the safety, efficacy or quality of the final product. The consequences of leaving any of the following issues unaddressed may compromise any benefit of utilizing stem cell-based products.

30 See Halme & Kessler, *supra* note 1 at 1730.

31 World Health Organization, *Meeting Report: WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products* (Geneva: WHO, 2007).

32 *Ibid.*

33 *Ibid.* at 5-6.

34 *Ibid.* at 6-7.

To begin, realizing the potential of stem cell technology will necessarily involve the development and expansion of cell lines. In order to ensure predictable safety risks in this context, cell lines must have stable characterizations.³⁵ Processes must then be implemented to ensure stem cells differentiate along the desired lineages, whether *in vitro* or *in vivo*.³⁶ Another essential consideration is the purity and potency of the stem cell-based product and the types of stem cells within.³⁷ Attention to these factors holds important implications for many of the following safety and efficacy issues.

A number of other issues arise during the handling and storage of stem cell-based products. First, there is a very real risk of product contamination. Cells or tissues may become contaminated at some stage in the process (e.g. handling or storage). The greater the extent of manipulation of such products, the greater this risk becomes, and many stem cell-based products would be highly manipulated. Contamination may occur at any time from stem cell derivation to storage to the eventual transplantation of the sample. Regulations reflecting the attention and caution required in manufacturing and handling such samples are necessary to minimize the risk of this occurring.³⁸

Another risk that presents itself at this stage is the potential for infection. Any cell or tissue product carries the risk of infection when transmitted from a donor to any eventual recipient. It may be inferred, then, that this risk significantly decreases in the context of autologous transplantation. The potential for infection in the allogeneic transplantation context, however, is significant. Because cell lines may be expanded to treat a much higher number of donors, the risk of infection is amplified.³⁹ Stem cell therapies

35 Liddell & Wallace, *supra* note 1 at 57; Chee-gee Liew *et al.*, "Human Embryonic Stem Cells: Possibilities for Human Cell Transplantation" (2005) 37 *Annals of Medicine* 521 at 527-28 (for the need to address the possibility of karyotypic changes prior to clinical trials in humans).

36 Halme & Kessler, *supra* note 1 at 1734; U.K., H.L., "Report from the Select Committee on Stem Cell Research," in *Sessional Papers* vol. 83(i) (2001-02), online: <<http://www.parliament.the-stationery-office.co.uk/pa/ld/ldstem.htm>> at para. 2.9 [H.L. "Report"]; Wobus & Boheler, *supra* note 6 at 661.

37 Halme & Kessler, *ibid.* at 1733; Lloyd-Evans, *supra* note 21 at 48.

38 Halme & Kessler, *ibid.* at 1732.

39 Peter Braude, Stephen L. Minger & Ruth M. Warwicke, "Stem cell therapy: hope or hype?" (2005) 330 *BMJ* 1159, online: <<http://www.bmj.com/cgi/content/full/330/7501/1159>>.

have the potential to transmit communicable, malignant, autoimmune and infectious diseases.⁴⁰ In order to manage this risk, extensive screening and testing of samples is required.⁴¹ Although not currently required, screening for predispositions to and family histories of serious genetic disease may also be advisable.⁴²

In the case of a xenographic transplant or where non-human animal cellular material is used in product development, the risk of infection includes the possible transmission of zoonoses (diseases that can be transmitted to humans from other animal species). This risk clearly exists in the context of xenotransplantation, where animal cells are transplanted into humans.⁴³ Safety regulations must therefore promote the definition of characteristics of the source animals and provide measures to prevent and monitor possible infections.⁴⁴ As technology evolves, the eventual screening and testing of animal tissues and cells will further assist in controlling risk of infection in this context.⁴⁵ The use of xenogeneic sources for scaffold material in tissue engineering may carry similar risks.⁴⁶ Even where the stem cell-based product contains only human cells, the risk of zoonotic infection may exist. For example, mouse feeder cells are commonly used in culture growth and differentiation of ES cells.⁴⁷ To ameliorate this, research-grade and clinical-grade stem cell lines must be kept separate; any reagents used in this process must also be safe for human use.⁴⁸ Strategies such as patient surveillance and developing a registry to oversee public health protection, in the context of monitoring the transmission of zoonotic agents, for example, have also been proposed.⁴⁹

40 *Ibid.*; Robert A. Preti, "Bringing Safe and Effective Cell Therapies to the Bedside" (2005) 23 *Nature Biotechnology* 801 at 801; Zubin Master, Marcus McLeod & Ivar Mendez, "Benefits, Risks and Ethical Considerations in Transplantation of Stem Cell Research to Clinical Applications in Parkinson's Disease" (2007) 33 *Journal of Medical Ethics* 169 at 172.

41 Halme & Kessler, *supra* note 1 at 1731.

42 *Ibid.*

43 Liddell & Wallace, *supra* note 1 at 56.

44 Tsang, *supra* note 1 at 1974; Rippon & Bishop, *supra* note 24 at 26.

45 Tsang, *ibid.*

46 Polak & Bishop, *supra* note 3 at 359.

47 H.L. "Report," *supra* note 36 at para. 3.7; Polak & Bishop, *ibid.* at 355-56.

48 Liddell & Wallace, *supra* note 1 at 56; Liew *et al.*, *supra* note 35 at 529.

49 Tsang, *supra* note 1 at 1974.

While screening for disease at the time samples are obtained is beneficial, it is insufficient. The storage process presents additional threats to the quality of samples, which must be addressed. First, the lifetime of samples is currently unknown, although it is foreseeable that sample viability will depend on both the content of the sample and storage conditions. A concrete risk in this context is revealed by evidence that stem cells may be damaged during the freezing and thawing inherent in the storage process.⁵⁰ As such, regulations specifying appropriate storage conditions are also necessary to preserve the viability of samples. In addition, elements used in the development process also have the potential to damage the final product. For example, antibiotics used to identify cells of interest in a culture or to manage contamination may interfere with inter-cell membrane communication or lead to antibiotic resistance.⁵¹ This risk must be quantified and managed appropriately.

Associated with the actual transplantation process are a number of additional safety, efficacy and quality concerns. It is as yet unclear to what extent the differentiation of stem cells and their integration into the intended site in the recipient's body can be reliably controlled in therapeutic applications involving direct administration and transplantation of differentiated stem cell progeny. There is a risk that the transplanted cells will fail to integrate as intended or undergo unintended integration. This includes ensuring the cells integrate with the desired tissue and perform the function intended.⁵² Failure to address this risk will not only compromise the efficacy of the product but may cause additional harm to the recipient.⁵³ Methods must be developed to ensure the cells integrate with the intended site,⁵⁴ and do not migrate to or integrate with unintended sites.⁵⁵ In addition, the concern of unintended differentiation present in the development context also applies at this stage.

50 Liddell & Wallace, *supra* note 1 at 57; Thomas Petersen & Laura Niklason, "Cellular Lifespan and Regenerative Medicine" (2007) 28 *Biomaterials* 3751 at 3754.

51 Liddell & Wallace, *ibid.* at 56.

52 Wobus & Boheler, *supra* note 6 at 661; Musina, Yegorov & Belyavsky, *supra* note 3 at 476.

53 Halme & Kessler, *supra* note 1 at 1733.

54 It will be critical to validate all types of differentiated progeny of ES cells for the ability to integrate fully and functionally with host tissue: Rippon & Bishop, *supra* note 24 at 28.

55 Master, McLeod & Mendez, *supra* note 40 at 171.

Currently, it is unclear to what extent this risk may be managed; it is clear that if left unaddressed, a risk of tumour formation may result. With cellular products, it is more difficult to define and ensure the degree of purity of the final product that is required for safety and quality, “mostly because of the lack of available technology to do so, the normal variability inherently characteristic of biological systems and the increased fragility of complex cell/tissue-based products.”⁵⁶

One of the fundamental features of stem cells, the potential for self-renewal, also poses a risk of tumorigenicity.⁵⁷ Tumour formation is a known risk particularly with the use of ES cells. Adult stem cells are believed to be safer, although “new observations of spontaneous transformation of human MSC [mesenchymal stem cells] during prolonged culture (4-5 months) argue for reassessment of the biosafety aspects of these cells.”⁵⁸ In certain circumstances, stem cells may divide to such an extent that tumours are formed. Residual undifferentiated cells that are administered to the patient along with differentiated cells may contribute to the formation of teratomas or tumours.⁵⁹ This indicates the need to ensure cell types are purified during the *in vitro* process.⁶⁰ Research suggests the risk of tumorigenicity increases with the amount of time prior to differentiation and transplantation of the stem cells. Genetic and epigenetic changes in stem cell lines, which accumulate over time, may affect both their capacity to differentiate and their tumorigenicity.⁶¹ Thus, appropriate limits on the length of time or number of generations must be determined in order to manage this risk. In addi-

56 Preti, *supra* note 40 at 802.

57 Halme & Kessler, *supra* note 1 at 1734; Wobus & Boheler, *supra* note 6 at 660 (for the fact that embryonic stem cells have many of the characteristics of cancer cells, which may explain their propensity to form teratomas and tetarocarcinomas) .

58 Polak & Bishop, *supra* note 3 at 357.

59 Liew *et al.*, *supra* note 35 at 528; Mark L. Rohrbaugh, “Intellectual Property Issues Surrounding Human Embryonic Stem Cells” in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington, D.C.: National Institutes of Health, 2006) 53 at 59, online: <<http://stemcells.nih.gov/info/scireport/2006report.htm>>.

60 Rippon & Bishop, *supra* note 24 at 30; *supra* note 28 at 50.

61 C. Allegrucci & L.E. Young, “Differences Between Human Embryonic Stem Cell Lines” (2007) 13 Human Reproduction Update 103 at 114; Daar & Sheremeta, *supra* note 3 at 8; Zwaka, *ibid.* at 50.

tion, attention to uncontrollable growth when testing the products in animal models is necessary.⁶² One difficulty, however, is that the risk of tumour formation may last for an extended period of time, exceeding the short life spans of the species generally used to test for such risks.⁶³

A third risk common to transplantation is immunological rejection,⁶⁴ which is most applicable to the allogeneic context where the donor and recipient are separate individuals, as the human body commonly rejects foreign tissues and cells. As a result, this occurrence must be suppressed in order to ensure the success of stem cell-based products. In general, the use of immuno-suppressant drugs, using matching tissues or using the individual's cells or tissues will alleviate this risk. Therefore, there is little risk of rejection in autologous transplantation.⁶⁵ However, autologous transplants are not always a practical option.⁶⁶ Nuclear transfer or genetic modification offer potential means of avoiding problems of immunogenicity,⁶⁷ but carry their own difficulties and risks.⁶⁸ Because stem cell-based products may consist of manipulated cells containing genetic material from the patient, it must be determined whether cell lines from cloned embryos should be considered autologous.⁶⁹ The answer to this question will affect how the risk of immune rejection will be characterized in the context of stem cell-based products. It has been suggested that this process – that is combining donor cell with patient genome – would reduce the need for immuno-suppressants with little risk of rejection and resulting infection.⁷⁰

62 Halme & Kessler, *supra* note 1 at 1734.

63 Master, McLeod & Mendez, *supra* note 40 at 171.

64 H.L. "Report," *supra* note 36 at para. 2.15; Wobus & Boheler, *supra* note 6 at 662; Rippon & Bishop, *supra* note 24 at 30; *ibid.*

65 Liddell & Wallace, *supra* note 1 at 56.

66 See e.g. Fodde, *supra* note 11 at 2183.

67 See e.g. Polak & Bishop, *supra* note 3 at 362; Committee on Guidelines for Human Embryonic Stem Cell Research *et al.*, *Guidelines for Human Embryonic Stem Cell Research* (Washington, D.C.: National Academies Press, 2005) at 34 [Committee on Guidelines, *Guidelines*].

68 Musina, Yegorov & Belyavsky, *supra* note 3 at 475; Daar & Sheremeta, *supra* note 3 at 8; Committee on Guidelines, *Guidelines, ibid.* at 35.

69 Liddell & Wallace, *supra* note 1 at 56; Wobus & Boheler, *supra* note 6 at 662: although the generation of autologous donor cells may raise additional legal and ethical issues. See also Rippon & Bishop, *supra* note 24 at 25.

70 Liew *et al.*, *supra* note 35 at 528-29; Rippon & Bishop, *ibid.* at 30; Jos Domen,

Finally, as explained, the development of stem cell-based products may entail procedures properly characterized as gene therapy – processes in which genes are modified or replaced to ameliorate genetic mutations.⁷¹ This will most commonly be seen where cells are manipulated in culture prior to transplantation. One of the inherent risks of gene therapy is the present inability to accurately predict and control all of the possible effects of modifying genes. In addition to its primary functional role, the therapeutic gene may also affect neighbouring genes. For example, certain mutations have been documented as contributing to malignant transformations of genes, ultimately resulting in cancer.⁷² Well-publicized adverse events in recent clinical trials have highlighted concerns about the safety of gene therapy.⁷³

These safety, efficacy and quality issues are present in current medical procedures. However, the nature of some of these concerns raised by stem cell therapy is distinct. In the context of stem cell-based products, regulations to manage and prevent these risks have not yet been comprehensively established. This is due in part to the evolving nature of stem cell technology. A failure to address these issues will compromise patient safety and health and may have significant legal consequences. Following the resolution of these important safety concerns, issues of clinical efficacy and product quality also need to be addressed. As a matter of policy, it will have to be determined what level of safety, efficacy and quality will be demanded of these products: that is, should stem cell-based therapies be required to have equivalent or better therapeutic potential compared with products currently on the market?⁷⁴ It is likely that the balance between risk and benefit will

Amy Wagers & Irving L. Weissman, "Bone Marrow (Hematopoietic) Stem Cells" in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington, D.C.: National Institutes of Health, 2006) 13 at 26, online: <<http://stemcells.nih.gov/info/scireport/2006report.htm>>.

71 Halme & Kessler, *supra* note 1 at 1734; Junying Yu & James A. Thomson, "Embryonic Stem Cells" in National Institutes of Health, eds., *Regenerative Medicine 2006* (Washington, D.C.: National Institutes of Health, 2006) 1 at 7, online: <<http://stemcells.nih.gov/info/scireport/2006report.htm>>.

72 Zwaka, *supra* note 28 at 47.

73 See e.g. J. Johnston & F. Baylis, "What Happened to Gene Therapy? A Review of Recent Events" (2004) 4:1 *Clinical Researcher* 11; J. Kimmelman, "Protection at the Cutting Edge: The Case for Central Review of Human Gene Transfer Research" (2003) 169 *Canadian Medical Association Journal* 781.

74 Liddell & Wallace, *supra* note 1 at 57.

vary between different types of products, and the relative benefits we expect may depend on the availability of alternative products.⁷⁵ These questions will therefore have to be assessed on a case-by-case basis.

2. Therapeutic Products Regulation and Stem Cell-Based Products

As the preceding discussion shows, the diverse stem cell-based products on the horizon carry enormous potential but also significant risks. As a result, it is important that they be appropriately regulated in order for their potential to be fulfilled and their risks minimized. Adequate regulatory requirements and oversight are essential to building public trust in these innovative products. At the same time, investments of time, energy and financial resources in the development of these products will be dependent on a regulatory regime that is clear, predictable and not unduly burdensome. The regulation of therapeutic products has become increasingly challenging as developing medical technology has increased the diversity and complexity of therapeutic products.

a. The Regulation of Therapeutic Products

The main categories of therapeutic products are drugs (also known as medicines or pharmaceutical drugs), biological products (also known as “biological drugs,” “biologicals” or “biologics”), and medical devices. In order for a product to be marketed in a particular jurisdiction, it must be approved in order to ensure that it is safe, effective for its intended use, and of sufficient quality. This involves regulation at three stages: pre-marketing evaluation, marketing approval, and post-marketing surveillance. The approval to market a product will require the submission of evidence of safety and efficacy. In order for this evidence to be sought through the conduct of clinical trials, the product will need to be administered to human subjects before it has been approved. Therefore, in the pre-marketing evaluation stage, limited use of the product for these purposes will be permitted, subject to approval by an ethics committee and/or the regulatory agency and in accordance with “good clinical practice” (GCP). Marketing approval will then be based on evaluation of the pre-clinical and clinical data. The particular manufacturers or distributors of the product will often have to be approved or licensed as well, to pro-

⁷⁵ Williams, *supra* note 22 at 26.

vide some assurance of the quality of their product. They are also required to adhere to “good manufacturing practices” (GMP). Finally, after a product has been approved and released onto the national market, the third stage involves post-marketing surveillance. This entails collecting reports of any adverse reactions and other monitoring of the product’s quality, efficacy, and safety. This describes the typical approach to regulating medicines or drugs; biologics are generally subject to some or all of the same requirements as well as other specific regulations. Medical devices tend to be regulated somewhat differently, with licensing requirements depending on risk classifications.

Therapeutic product regulation exists alongside other regulatory regimes that affect the development, distribution, and use of the products. Therapeutic products may be protected by patents and the protection of patent rights may be linked to the regime for marketing approvals.⁷⁶ Medical research may be subject to legal and administrative controls beyond the requirements of GCP imposed within the therapeutic products regime. The creation or procurement of embryos as potential sources of stem cells is subject to specific regulation under assisted reproduction legislation in Canada and other jurisdictions.⁷⁷ This legislation regulates the manipulation, handling and storage of embryos, and it limits the purposes for which embryos may be created.⁷⁸ It also specifies the consent requirements applicable to donors of reproductive material.⁷⁹ The procurement and use of human tissue for transplantation is also subject to specific legislation, though in Canada, such legislation applies only to types of human tissue that do not

76 See e.g. *Patented Medicines (Notice of Compliance) Regulations*, S.O.R./93-133.

77 *Assisted Human Reproduction Act*, R.S.C. 2004, c.2 [AHRA]. In the U.K., see: *Human Fertilisation and Embryology Act 1990* (U.K.), 1990, c. 37; *The Human Fertilisation and Embryology (Quality and Safety) Regulations 2007*, S.I. 2007/1522. A draft bill released in May 2007 would revise this legislation in the U.K.: Department of Health, *Human Tissue and Embryos (Draft) Bill: Draft revised legislation for assisted reproduction and embryo research (including establishment of the Regulatory Authority for Tissue and Embryos)* (May 2007), online: <http://www.dh.gov.uk/prod_consum_dh/idcplg?IdcService=GET_FILE&dID=140183&Rendition=Web>.

78 *AHRA*, *ibid.*, s. 5(1)(b): *In vitro* embryos may not be created for purposes other than creating a human being or improving or providing instruction in assisted reproduction procedures.

79 *Ibid.*, s. 8. Regulations setting out further details were recently promulgated and are in force as of December 2007: *Assisted Human Reproduction (Section 8 Consent) Regulations*, S.O.R./2007-137.

naturally self-repair.⁸⁰ Where it does apply, this legislation addresses consent requirements and prohibits the sale of human tissue for transplantation.⁸¹ Its application in the context of stem cell-based products is likely limited but where relevant it may be an important consideration. Finally, the availability of specific products, once they have been granted marketing approval, is affected by rules determining how products may be sold (e.g. prohibited, prescription-only, or over-the-counter products), and which products will be publicly funded. The focus of this article is on therapeutic products regulation, however it is important to be aware of these other aspects of the regulatory context.

b. Regulatory Framework in Canada

Therapeutic products are regulated by the Health Products and Food Branch (HPFB) of Health Canada under the authority of the *Food and Drugs Act* (FDA)⁸² and *Food and Drug Regulations* (FDR).⁸³ Within the HPFB, the Therapeutic Products Directorate (TPD) is responsible for the regulation of pharmaceutical drugs and medical devices, while the Biologics and Genetic Therapies Directorate (BGTD) regulates biological drugs (biologics), genetic therapies and radiopharmaceutical products.

80 *The Human Tissue Gift Act*, R.S.S. 1978, c. H-5 [HTGA]; *Human Tissue and Organ Donation Act*, S.A. 2006, c. H-14.5 [HTODA] (awaiting proclamation); *Trillium Gift of Life Network Act*, R.S.O. 1990, c. H.20 [TGLNA]. The definition of tissue in the context of this legislation does not include skin, bone, blood, blood constituent or other tissue that is replaceable by natural processes of repair: HTGA, s. 2(c). For human tissue regulations in the United States jurisdiction, see 42 U.S.C. 6A § 289g [*The Public Health and Welfare*] and 21 C.F.R., part 1270 [*Food and Drugs, Regulations*]; in the U.K. see *Human Tissue Act 2004* (U.K.), 2004, c. 30. For discussion of the U.K. legislation see: Liddell & Wallace, *supra* note 1 at 60-61. The *Human Tissue and Embryos (Draft) Bill*, *supra* note 77, would also amend the *Human Tissue Act 2004*.

81 HTGA, *ibid.*, s. 11; HTODA, *ibid.*, s. 10; TGLNA, *ibid.*, s. 10. One question that arises is whether this prohibition applies to engineered tissue. This appears to be the case on the face of the legislation, though this likely would not have been contemplated by the drafters of the legislation.

82 *Food and Drugs Act*, R.S.C. 1985, c. F-27 [FDA].

83 *Food and Drug Regulations*, C.R.C., c. 870 [FDR].

The FDA defines a “device” and a “drug” as follows:

“device” means any article, instrument, apparatus or contrivance, including any component, part or accessory thereof, manufactured, sold or represented for use in

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- (b) restoring, correcting or modifying a body function or the body structure of human beings or animals,
- (c) the diagnosis of pregnancy in human beings or animals, or
- (d) the care of human beings or animals during pregnancy and at and after birth of the offspring, including care of the offspring.

and includes a contraceptive device but does not include a drug;

“drug” includes any substance or mixture of substances manufactured, sold or represented for use in

- (a) the diagnosis, treatment, mitigation or prevention of a disease, disorder or abnormal physical state, or its symptoms, in human beings or animals,
- (b) restoring, correcting or modifying organic functions in human beings or animals, or
- (c) disinfection in premises in which food is manufactured, prepared or kept.⁸⁴

Biological drugs are listed in Schedule D to the FDA and include “blood and blood derivatives, except cord blood and peripheral blood that are a source of lymphohematopoietic cells for transplantation,” “drugs obtained by recombinant DNA procedures,” and “drugs, other than antibiotics, prepared from micro-organisms.” These products are subject to regulations in Part C, Division 4 of the FDR with respect to the premises, process and conditions of manufacture, and are otherwise regulated as drugs.

84 FDA, *supra* note 82, s. 2.

Clinical trials for drugs must conform to Good Clinical Practices (GCP)⁸⁵ and the requirements set out in the FDR.⁸⁶ Medical device clinical trials must conform to Canada's *Medical Devices Regulations* (MDR).⁸⁷ Drugs (including biological drugs) must be approved for marketing following an assessment of safety, efficacy and quality. Drugs marketed in Canada are subject to product labelling requirements and Good Manufacturing Practices (GMP),⁸⁸ and establishments handling pharmaceutical or biological drugs must be licensed. Health Canada (through the Canadian Adverse Drug Reaction Monitoring Program) collects information about adverse reactions to drugs and biologics, and where necessary will issue an advisory, warning or recall of these products. Manufacturers are required to report serious adverse drug reactions of which they become aware.⁸⁹

All medical devices are subject to safety and effectiveness requirements, which require manufacturers to identify and eliminate or reduce risks, and ensure that the device will perform as intended and be effective.⁹⁰ For the purposes of licensing requirements, medical devices are classified according to their level of risk.⁹¹ Class II, III, and IV medical devices must be issued a Medical Device Licence prior to being marketed; the information required for the licence application depends on the class of device and will include data on safety, efficacy and quality.⁹² Establishments selling or importing medical devices must also be licensed.⁹³ Any "problems" with medical de-

85 *FDR*, *supra* note 83, s. C.05.010; International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice E6(R1)* (Geneva: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1996), online: <<http://www.ich.org/LOB/media/MEDIA482.pdf>>.

86 *FDR*, *ibid.*, Part C, Division 5.

87 S.O.R./98-282 [*MDR*].

88 Health Products and Food Branch Inspectorate, *Good Manufacturing Practices Guidelines 2002 Edition Version 2* (Ottawa: Health Canada, 2003), online: <http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/compli-conform/2002v2_e.pdf>.

89 *FDR*, *supra* note 83, s. C.01.016.

90 *MDR*, *supra* note 87, ss. 9-10.

91 *Ibid.*, s. 6, Schedule 1.

92 *Ibid.*, ss. 26, 32.

93 *Ibid.*, s. 44.

vices, including the failure or deteriorating effectiveness of a device that has caused or could cause serious health consequences, must be reported by the manufacturer.⁹⁴

New regulations dealing with human cells, tissues and organs (CTO) came into force in December 2007.⁹⁵ These *CTO Regulations* only apply to “organs and minimally manipulated cells and tissues.”⁹⁶ “Minimally manipulated” is defined as:

(a) in respect of a structural tissue, that the processing does not alter the original characteristics that are relevant to its claimed utility for reconstruction, repair or replacement; and

(b) in respect of cells and nonstructural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility.⁹⁷

The *CTO Regulations* do *not* apply to certain products, including:

(a) cells, tissues and organs that are for non-homologous use;

(b) cells, tissues and organs that are for autologous use;

...

(d) tissues and cells – except for islet cells, and except for lymphohematopoietic cells that are derived from bone marrow, peripheral blood or cord blood – that have a systemic effect and depend on their metabolic activity for their primary function;

(e) medical devices that contain cells or tissues and that are the subject of investigational testing involving human subjects under Part 3 of the *Medical Devices Regulations*;

94 *Ibid.*, s. 59.

95 *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*, S.O.R./2007-118 [*CTO Regulations*]. The provision dealing with *in vitro* diagnostic devices will come into force in June 2008: s. 26(1).

96 *Ibid.*, s. 2.

97 *Ibid.*, s. 1. Further elaboration is provided in Health Canada, *Draft Guidance Document: Safety of Human Cells, Tissues and Organs for Transplantation* (Ottawa: Policy and Promotion Division, Biologics and Genetic Therapies Directorate, 2007) at 15-16 [*Health Canada, CTO Draft Guidance Document*].

(f) cells, tissues and organs that are the subject of clinical trials under Division 5 of Part C of the *Food and Drug Regulations*;

(g) Class IV medical devices that are regulated under the *Medical Devices Regulations*;

...

(i) cells and tissues that are regulated under the *Assisted Human Reproduction Act* or any of its regulations

...⁹⁸
...

CTO that are subject to these regulations are exempt from other FDA regulations.⁹⁹ The *CTO Regulations* require establishments that process CTO to be registered.¹⁰⁰ They also set out requirements for donor suitability, processing, testing, packaging, labelling, storage, and distribution of CTO; for the investigation and reporting of error, accidents, and adverse events; and for establishment personnel, facilities, equipment and supplies.

Human cells, tissues, and cell- or tissue-based products that do not fall within the scope of the *CTO Regulations* will be regulated as drugs, biologics or medical devices. The draft Guidance Document on the *CTO Regulations* states that any products currently regulated as drugs or medical devices will continue to be regulated as such, and any cells or tissues “combined with non-tissue products such as artificial elements used for tissue engineering” will fall outside the scope of these regulations.¹⁰¹ At the same time the *CTO Regulations* were registered, other regulations amended the FDA and MDR to clarify their scope. The definition of biologics in Schedule D to the FDA was amended to exclude “cord blood and peripheral blood that are a source of lymphohematopoietic cells for transplantation” from the blood and blood products that otherwise fall within biologics.¹⁰² Cord blood and peripheral blood intended for transfusion remain covered by Schedule D. The MDR were also amended to provide that a medical device “that is manufactured from or that incorporates human or animal cells or tissues or their derivatives” or “that is manufactured from or that incorporates a prod-

98 *CTO Regulations, ibid.*, s. 3(1).

99 *Ibid.*, s. 3(2).

100 *Ibid.*, ss. 4-5.

101 Health Canada, *CTO Draft Guidance Document, supra* note 97 at 19.

102 *Supra* note 82, Schedule D (as amended). See *Regulations Amending Schedule D to the Food and Drugs Act (Blood and Blood Derivatives)*, S.O.R./2007-120.

uct produced through the use of recombinant DNA technology” is a Class IV medical device (unless it is intended to come into contact with intact skin only).¹⁰³ Class IV is the highest-risk classification and licensing requires the submission of more extensive information and documents, including detailed information on safety and effectiveness.¹⁰⁴

Determining which product categories and regulations apply to stem cell-based products requires a close examination of the definitions and scopes of application in the legislation and the characteristics of particular products. Depending on the type of stem cell-based product, different provisions will apply. It is expected that most of these products will be excluded from the *CTO Regulations* on the basis that they are more than minimally manipulated, involve autologous use, or involve non-homologous use. A stem cell-based product will then be regulated as a drug (if it can be characterized as a “substance”) or a device (if it can be characterized as an “article, instrument, apparatus, or contrivance”). Some products classified as drugs, especially those involving genetic manipulation, may also fall within the definition of biologics.¹⁰⁵ Engineered tissue containing or created using stem cells would likely be considered a Class IV medical device. Even if the final product does not contain non-tissue materials (such as a scaffold or matrix), it would still fall outside the scope of the *CTO Regulations* because the cells and tissues have been more than minimally manipulated. Where it is not clear which product category should apply, this will be determined by the TPD, with input from the manufacturer.¹⁰⁶

103 *Supra* note 87, Schedule 1, Part 1, Rule 14 (as amended). See *Regulations Amending the Medical Devices Regulations*, S.O.R./2007-119.

104 *MDR, ibid.*, s. 32(4).

105 Keith Bailey & Anthony Ridgway, “A Rational Approach to Regulation of Gene Therapy in Canada” (1996) 17 *Transfusion Science* 197 at 200. See also Health Canada, “Products” (23 March 2006), online: <http://www.hc-sc.gc.ca/sr-sr/biotech/health-prod-sante/products-produits_e.html>, which lists gene therapy and “cell therapy products” among the biotechnology products that are biologics.

106 Bailey & Ridgway, *ibid.*

c. Regulatory Frameworks in Other Jurisdictions

United States

In the United States, the Federal Food and Drug Administration (USFDA) is responsible for the regulation of therapeutic products such as drugs, devices or biological products. Its primary source of authority is the *Federal Food, Drug and Cosmetic Act*.¹⁰⁷ To determine which regulations apply, it is necessary to characterize the product as a drug, device, biological or combination product. A drug is defined to include:

- (A) articles recognized in the official United States Pharmacopoeia, official Homoeopathic Pharmacopoeia of the United States, or official National Formulary, or any supplement to any of them; and
- (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals; and
- (C) articles (other than food) intended to affect the structure or any function of the body of man or other animals....¹⁰⁸

New drugs must be approved on the basis of an application that includes evidence of safety and efficacy, a statement of its components and composition, and a description of the methods, facilities and controls used in its production.¹⁰⁹ Drugs must be produced, packaged, and stored in accordance with GMP.¹¹⁰

A device is defined as:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is—

- (1) recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

107 21 U.S.C., Chapter 9 [*Food and Drugs*].

108 *Ibid.*, § 321(g)(1).

109 *Ibid.*, § 355.

110 *Food and Drugs, Regulations, supra* note 80, part 210.

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes.¹¹¹

Devices are divided into three classes depending on the level of control required. Class I devices are subject only to general controls; class II devices are subject to “special controls” such as performance standards and post-market surveillance; and class III devices require pre-market approval (unless exempted).¹¹² A class III device is one that may require more than general or special controls and is represented to be life-supporting or life-sustaining, or “for a use which is of substantial importance in preventing impairment of human health,” or “presents a potential unreasonable risk of illness or injury.”¹¹³ Pre-market approval of class III devices requires the submission of information on safety, efficacy, quality and other matters,¹¹⁴ similar to the requirements for pre-market approval of a drug.

Biological products are specific types of drugs, defined to include “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”¹¹⁵ Biological products must be licensed before they can be marketed.¹¹⁶ Although they are regulated under the authority of the *Public Health and Welfare Act*,¹¹⁷ under a provision of this Act they are made subject

111 *Food and Drugs*, *supra* note 107, § 321(h).

112 *Ibid.*, § 360c; *Food and Drugs, Regulations*, *supra* note 80, § 860.3(c).

113 *Food and Drugs*, *ibid.*, § 360c; *Food and Drugs, Regulations*, *ibid.*, § 860.3(c)(3).

114 *Food and Drugs, Regulations*, *ibid.*, § 360e(c).

115 *The Public Health and Welfare*, *supra* note 80, § 262(i).

116 *Ibid.*, § 262(a). For licensing requirements, see *Food and Drugs, Regulations*, *supra* note 80, part 601.

117 *The Public Health and Welfare*, *ibid.*

to the *Federal Food, Drug and Cosmetic Act*.¹¹⁸ Standards relating to safety, potency, purity and other matters are prescribed under the latter Act.¹¹⁹

A combination product contains two or more different regulated components (e.g. a drug and device or biologic and device).¹²⁰ The Office of Combination Products was established to coordinate the review of such products, including designation of products as combination products, assignment of a lead centre with primary jurisdiction, and coordination of timely and consistent pre-market and post-market evaluation.¹²¹ The lead centre will be assigned based on the product's "primary mode of action", meaning the "most important therapeutic action of the combination product."¹²²

The United States, like Canada, has recently adopted new regulations regarding human cell, tissues, and cell- or tissue-based products (HCT/Ps).¹²³ HCT/Ps are defined as:

articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.¹²⁴

There are a few situations in which HCT/Ps will be exempt from these regulations, such as when they are removed from an individual and implanted into the same individual as part of the same surgical procedure.¹²⁵

118 *Ibid.*, § 262(j).

119 *Food and Drugs, Regulations*, *supra* note 80, part 610.

120 *Ibid.*, §3.2(e).

121 *Food and Drugs*, *supra* note 107, § 353(g).

122 *Food and Drugs, Regulations*, *supra* note 80, § 3.2(m).

123 *Human Cells, Tissues, and Cellular and Tissue-Based Products Regulations*, 21 C.F.R., Part 1271 [*Tissue-Based Products Regulations*].

124 *Ibid.*, § 1271.3(d). Certain articles are excluded from the definition of HCT/P, such as: vascularized human organs for transplantation; whole blood or blood derivatives or components subject to other regulations; and minimally manipulated bone marrow for homologous use and not combined with another article.

125 *Ibid.*, § 1271.15(b).

Otherwise, HCT/Ps are subject to the *HCT/Ps Regulations* but do not need to be licensed if they meet all of the following criteria:

- (1) The HCT/P is minimally manipulated;
- (2) The HCT/P is intended for homologous use only, as reflected by the labelling, advertising, or other indications of the manufacturer's objective intent;
- (3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and
- (4) Either:
 - (i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
 - (ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 - (a) Is for autologous use;
 - (b) Is for allogeneic use in a first-degree or second-degree blood relative; or
 - (c) Is for reproductive use.¹²⁶

These products are deemed to present a lesser risk to public health and safety, and therefore are subject to less stringent regulation.¹²⁷ They must comply with the "good tissue practices" (GTP) set out in the *HCT/Ps Regulations*,¹²⁸ which deal with such matters as facilities, processing, supplies and reagents, storage, and donor eligibility.

HCT/Ps that do not meet the criteria set out above are also subject to the GTP, but in addition, they will be regulated as drugs, devices, or biological products.¹²⁹ Stem cell-based products would generally fall into these

126 *Ibid.*, § 1271.10(a).

127 Preti, *supra* note 40 at 803.

128 *Tissue-Based Products Regulations*, *supra* note 123, Subparts D, E and F.

129 *Ibid.*, §1271.20.

categories, because they will be more than minimally manipulated. Most stem cell-based products would be considered biologics,¹³⁰ including those that are considered to be gene therapy products.¹³¹ Some stem cell-based products, especially engineered tissue where its function is predominantly structural and does not depend on chemical or metabolic activity, could also be considered devices or combination products.¹³²

European Union

The European Medicines Agency (EMA) and relevant national agencies are responsible for the authorization and supervision of medical products. In the relevant directive (Medicinal Products Directive), a medicinal product is defined as:

- (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
- (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.¹³³

The “substance” referred to in this definition may be “[a]ny matter irrespective of origin,” including human, animal, vegetable or chemical origin.¹³⁴ Subject to certain exemptions,¹³⁵ all medicinal products require marketing authorization prior to being placed on the market in any member state.¹³⁶ An application for marketing authorization requires submission of the usual

130 Halme & Kessler, *supra* note 1 at 1731, Table 1.

131 USFDA, “Human Gene Therapy and the Role of the Food and Drug Administration” (24 March 2003), online: <http://www.fda.gov/cber/infosheets/genezn.htm>.

132 Preti, *supra* note 40 at 803; Lloyd-Evans, *supra* note 21 at 51. See the definition of device, *supra* note 111 and accompanying text.

133 EC, *Council Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community Code Relating to Medicinal Products for Human Use*, [2001] O.J. L 311/67, art. 1(2), as amended [EC, *Council Directive 2001/83/EC*].

134 *Ibid.*, art. 1(3).

135 *Ibid.*, art. 3.

136 *Ibid.*, art. 6.

categories of information including manufacturing methods, control methods, and results of tests and clinical trials.¹³⁷

The European Union has two processes for marketing authorization: centralized and decentralized. The decentralized (mutual recognition) procedure allows companies to apply for marketing authorization in one EU member state and then submit an identical dossier to other member states. The first state will send its assessment report to the other states, which then have ninety days to decide whether to recognise the approval. The centralized procedure involves a single application to the EMEA, with a positive opinion of the EMEA having the effect of a marketing authorization for the whole of the EU. The centralized procedure is mandatory for certain products, notably those that have been manipulated in a way that alters their gene expression, and optional for other therapeutic products.¹³⁸ Centralized authorization does not affect “the powers of Member States’ authorities as regards setting the prices of medicinal products or their inclusion in the scope of national health system or social security schemes,”¹³⁹ and member states are permitted “exceptionally to prohibit the use in their territory of medicinal products for human use which infringe objectively defined concepts of public policy and public morality,”¹⁴⁰ in particular contraceptives or abortifacients.¹⁴¹

Medical devices are governed by a separate directive (Medical Devices Directive),¹⁴² which defines a medical device as:

any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, ... intended by the manufacturer to be used for human beings for the purpose of:

– diagnosis, prevention, monitoring, treatment or alleviation of disease,

137 *Ibid.*, art. 8.

138 EC, *Council Regulation (EC) 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency*, [2004] O.J. L 136/1, art. 3 [EC, *Council Regulation (EC) 726/2004*].

139 *Ibid.*, art. 1.

140 *Ibid.*, cl. 13.

141 EC, *Council Directive 2001/83/EC*, *supra* note 133, art. 4(4).

142 EC, *Council Directive 93/42/EEC of 14 June 1993 concerning medical devices*, [1993] O.J. L 169/1 [EC, *Council Directive 93/42/EEC*].

- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
- investigation, replacement, or modification of the anatomy or of a physiological process,
- control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.¹⁴³

The Medical Devices Directive does not, however, apply to human or animal tissues or cells, or products incorporating or derived from them.¹⁴⁴

A 2004 directive (Tissues and Cells Directive) sets quality and safety standards for human tissues and cells used for therapeutic purposes, covering all stages from donation to processing, storage and distribution.¹⁴⁵ It applies to all human cells or tissues intended to be used in human applications, except autologous grafts within the same surgical procedure, blood and blood components, and organs (or parts of organs if they are to be used for the same purpose as entire organs).¹⁴⁶ Where products manufactured from human cells or tissues are covered by other directives, the Tissues and Cells Directive only applies to donation, procurement and testing.¹⁴⁷ The Directive requires Member States to ensure that establishments handling

143 *Ibid.*, art. 1(2)(a), as amended by EC, *Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market*, [2007] O.J. L 247/21. A separate directive governs “active implantable medical devices,” meaning those which use a source of power other than the human body or gravity, and are inserted into the body or a natural orifice of the body: EC, *Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices*, [1990] O.J. L 189/17, art. 1(2).

144 EC, *Council Directive 93/42/EEC, ibid.*, art. 1(5).

145 EC, *Council 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*, [2004] O.J. L 102/48 [EC, *Council Directive 2004/23/EC*].

146 *Ibid.*, art. 2(2).

147 *Ibid.*, art. 2(1).

human tissues are accredited, designated, authorised or licensed by a competent authority.¹⁴⁸ Article 8 imposes traceability requirements for all tissues and cells.¹⁴⁹ Chapter III governs donor selection and evaluation, including consent and confidentiality. Chapter IV sets out requirements for ensuring quality and safety.

The most recent development in the European regime, which is of direct relevance for stem cell-based products, is the 2007 adoption of a new regulation governing “advanced therapy medicinal products.”¹⁵⁰ It will apply to gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products.¹⁵¹ Tissue engineered products are defined as products containing engineered cells or tissues, for use in “regenerating, repairing or replacing a human tissue.”¹⁵² They may contain human or animal cells or tissues (or both), and may contain other substances such as scaffolds or matrices.¹⁵³ “Engineered” cells and tissues are those which “have been subject to substantial manipulation” and/or which are “not intended to be used for the same essential function or functions in the recipient as the donor” (i.e. non-homologous use).¹⁵⁴ The amended annex to Directive 2001/83/EC defines a gene therapy medicinal product as “a product obtained through a set of manufacturing processes aimed at the transfer, to be performed either *in vivo* or *ex vivo*, of a prophylactic, diagnostic or therapeutic gene (i.e. a piece of nucleic acid), to human/animal cells and its subsequent expression *in vivo*.”¹⁵⁵ Somatic cell medicinal products are defined as “the use in humans

148 *Ibid.*, art. 6.

149 *Ibid.*, art. 8.

150 EC, *Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products and Amending Directive 2001/83/EC and Regulation (EC) No 726/2004*, [2007] O.J. L324/121 [ATMP Regulation]. The proposed regulation was agreed to by the European Council in May 2007 and formally adopted in October 2007; it will apply from 30 December 2008: European Commission, “Advanced Therapies: Tissue Engineering, Cell Therapy and Gene Therapy” (9 January 2008), online: <<http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm>>.

151 *ATMP Regulation, ibid.*, art. 2(1)(a).

152 *Ibid.*, art. 2(1)(b).

153 *Ibid.*, art. 2(1)(b). Products “which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action” are excluded.

154 *Ibid.*, art. 2(1)(c).

155 EC, *Council Directive 2001/83/EC, supra* note 133, Annex I, Part IV, 1.

of autologous..., allogeneic..., or xenogeneic... somatic living cells, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventive effect through metabolic, pharmacological and immunological means."¹⁵⁶

Donation, procurement and testing of the cells and tissues used in these products will be governed by the Tissues and Cells Directive.¹⁵⁷ Marketing authorizations for advanced therapy medicinal products will be dealt with under the centralized procedure, with the EMEA consulting a newly established Committee on Advanced Therapies in its evaluation of a product.¹⁵⁸ Traceability requirements are imposed on all of the materials in a product, including starting and raw materials and all substances that come into contact with cells or tissues that may be contained in the product.¹⁵⁹ The final products and patients who receive them must also be traceable.¹⁶⁰

Guidelines on good clinical practice and good manufacturing practice for advanced therapy medicinal products are to be developed.¹⁶¹ The EMEA has released a draft Guideline on Human Cell-Based Medicinal Products, which applies to viable human cells of allogeneic and autologous origin, cells combined with non-cellular components and genetically modified cells.¹⁶² It is intended to address "development, manufacturing and quality control as well as non-clinical and clinical development of cell-based medicinal products."¹⁶³ It recognizes that the "risk posed by the administration of a cell-based medicinal product is highly dependent on the origin of the cells, the manufacturing process, the non-cellular components and on the specific therapeutic use."¹⁶⁴

It can be expected that most stem cell-based products will be governed by the new advanced therapy medicinal products regulation, as gene therapy medicinal products, somatic cell therapy medicinal products, or tissue engi-

156 *Ibid.*, Annex I, Part IV, 2.

157 *ATMP Regulation*, *supra* note 150, art. 3.

158 *Ibid.*, art. 8.

159 *Ibid.*, art. 15(1).

160 *Ibid.*, art. 15(2).

161 *Ibid.*, arts. 4(2), 5.

162 EMEA, *Guideline on Human Cell-Based Medicinal Products* (London: Committee for Human Medicinal Products, 2007) [EMEA, *Guideline*].

163 *Ibid.* at 3.

164 *Ibid.* at 4.

neered products.¹⁶⁵ They will therefore be subject to provisions on donation, procurement and testing in the Tissues and Cells Directive, and will require marketing authorization from the EMEA under the centralized procedure. Given the differences of opinion among EU Member States on the use of ES cells, the proposed regulation does not address this issue, and therefore “the use or prohibition of [advanced therapy medicinal products] containing certain types of cells (such as embryonic stem cells) ... would remain a national responsibility.”¹⁶⁶

Australia

The Therapeutic Goods Administration (TGA) is responsible for the testing, licensing and monitoring of all therapeutic products and medicines, under the *Therapeutic Goods Act 1989*¹⁶⁷ and its regulations. There are two main categories of therapeutic goods: medicines and medical devices. Medicines are defined as “therapeutic goods that are represented to achieve, or are likely to achieve, their principal intended action by pharmacological, chemical, immunological or metabolic means in or on the body of a human or animal”.¹⁶⁸ Medicines must either be “registered” or “listed” according to their characteristics and level of risk.¹⁶⁹ The process for registration is equivalent to marketing authorization in other jurisdictions, involving submission of evidence as to safety, efficacy and quality.

A new regulatory regime governing medical devices has recently been adopted, and the transition period ended in October 2007. A medical device is defined as:

165 If products fall within the definition of both somatic cell therapy medicinal products and tissue engineered products they will be considered tissue engineered products; if they fall within all three categories they will be considered gene therapy medicinal products: *ATMP Regulation*, *supra* note 150, arts. 2(4)-(5).

166 Medicines and Healthcare Products Regulatory Agency, Press Release, “New European Regulation on Tissue Engineering to Benefit Patients” (1 June 2007), online: MHRA <http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON2031317&RevisionSelectionMethod=LatestReleased> at 6. See *ATMP Regulation*, *supra* note 150, cl. 7.

167 *Therapeutic Goods Act 1989* (Cth.) [TGA].

168 *Ibid.*, s. 3(1).

169 *Therapeutic Goods Regulations 1990* (Cth.), Sch. 3 and 4 [TGR].

(a) any instrument, apparatus, appliance, material or other article (whether used alone or in combination, and including the software necessary for its proper application) intended, by the person under whose name it is or is to be supplied, to be used for human beings for the purpose of one or more of the following:

(i) diagnosis, prevention, monitoring, treatment or alleviation of disease;

(ii) diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

(iii) investigation, replacement or modification of the anatomy or of a physiological process;

(iv) control of conception;

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

(b) an accessory to such an instrument, apparatus, appliance, material or other article.¹⁷⁰

Medical devices are divided into five classifications, depending on their intended use, level of risk and degree of invasiveness.¹⁷¹ Medical devices must comply with “essential principles” relating to matters including health and safety, minimizing risks, suitability for intended purpose, and design and construction.¹⁷² Standards may also be prescribed for particular types of medical devices.¹⁷³ Manufacturers are required to apply “conformity assessment procedures,” which vary according to the class of device.¹⁷⁴ Some kinds

170 *Ibid.*, s. 41BD(1).

171 Therapeutic Goods Administration, *Australian Medical Devices Guidelines: An Overview of the New Medical Devices Regulatory System (Guidance Document Number 1)* (Woden: Therapeutic Goods Administration, 2003) at 9 [TGA, *Guidelines*]. See *Therapeutic Goods (Medical Devices) Regulations 2002* (Cth.), r. 3.2 and Sch. 2 [TGMDR].

172 TGA, *supra* note 167, s. 41CA; TGMDR, *ibid.*, Sch. 1.

173 TGA, *ibid.*, s. 41CB.

174 *Ibid.*, s. 41DA; TGMDR, *supra* note 171, Sch. 3.

of devices require certification of these procedures before an application can be made for registration of the device.¹⁷⁵

Fresh, viable organs and tissues used in “direct donor-to-host transplantation” are excluded from the requirements for therapeutic goods.¹⁷⁶ Human tissue that is “obtained, stored and supplied without any deliberate alteration to its biological or mechanical properties” must comply with the *Australian Code of Good Manufacturing Practice – Human Blood and Tissues*,¹⁷⁷ but does not need to be registered.¹⁷⁸ Other human tissues and cell- and tissue-based products are regulated either as medicines or medical devices. If the product’s principal therapeutic purpose is “achieved through chemical, pharmacological, or metabolic actions’ and it is “generally able to be batch released”, it will be considered a medicine.¹⁷⁹ Devices of “human origin,” that is those “manufactured” from human tissue, are presently designated as “other therapeutic goods” and will remain under the old system of regulation of “therapeutic devices” rather than the new regime for medical devices, and registration will be required.¹⁸⁰

Under the current regulatory framework, stem cell-based products would likely be considered medicines (requiring registration) or therapeutic devices. However, a new regulatory regime for human cellular and tissue therapies (HCTs) is under development in Australia.¹⁸¹ Reform is believed

175 *TGMDR, ibid.*, r. 4.1.

176 *Therapeutic Goods (Excluded Goods) Order No. 1 of 2005* (Cth.), s. 2(o).

177 Therapeutic Goods Administration, *Australian Code of Good Manufacturing Practice – Human Blood and Tissues* (Woden: Therapeutic Goods Administration, 2000).

178 *TGR, supra* note 169, Sch. 5, Item 7(q).

179 Therapeutic Goods Administration, “Regulation of Tissues” (25 October 2004), online: <<http://www.tga.gov.au/bt/tissues.htm>>.

180 TGA, *Guidelines, supra* note 171 at 7; Therapeutic Goods Administration, *Australian Medical Devices Guidance Document Number 35: Device-Medicine Boundary Products* (Woden: Therapeutic Goods Administration, 2005) at 10.

181 Therapeutic Goods Administration, *Discussion Paper: The Regulation of Human Tissues and Emerging Biological Therapies* (Woden: Therapeutic Goods Administration, 2003); Therapeutic Goods Administration and MedSafe (New Zealand), *Consultation Paper: The Regulation of Human Cellular and Tissue Therapies under the Australia New Zealand Therapeutic Products Authority (ANZTPA)* (Woden: Therapeutic Goods Administration, 2007) [TGA, *Consultation Paper*]. Note that the new framework was to have been adopted by a joint regulatory authority established by agreement with New Zealand, which is presently on hold: see Annette King, “Therapeutic Products and Medicines Bill on Hold” (16 July 2007),

to be desirable in order to minimize risks, provide for “greater regulatory certainty” and harmonization with international requirements, and adopt a risk-based approach to regulation.¹⁸² It is proposed that HCTs be divided into four classes according to a “risk benefit analysis.”¹⁸³ Most stem cell-based products would likely fall within class four, that is, cells or tissues processed:

- (a) so that the biological properties are deliberately manipulated; or
- (b) for a purpose for which the cell or tissue is intended to be used is not its usual biological function [i.e. non-homologous use].¹⁸⁴

Examples given in the consultation paper include cells “subject to genetic manipulation” and “blood stem cells when used for myocardial repair.”¹⁸⁵ These products would require a manufacturing licence (after showing compliance with manufacturing principles and relevant standards) and demonstration of safety, efficacy and quality, as evidenced by clinical data and analysis.¹⁸⁶ Adverse event reporting and regulation of clinical trials (e.g. GCP) would also apply to HCTs.¹⁸⁷

3. Potential Issues and Challenges in Regulating Stem Cell-Based Products

This survey of regulatory regimes highlights several issues which may arise with respect to the regulation of stem cell-based products. These include variations between the regulatory frameworks of different jurisdictions, lack of clarity about appropriate product categories for stem cell-based products, issues in the application of regulatory requirements to stem cell-based products, and the relationship between product regulation and ethical, legal and social issues.

online: New Zealand Government

<<http://www.beehive.govt.nz/ViewDocument.aspx?DocumentID=30061>>.

182 TGA, *Consultation Paper*, *ibid.* at 8.

183 *Ibid.* at 11.

184 *Ibid.*

185 *Ibid.* at 16.

186 *Ibid.* at 12.

187 *Ibid.* at 13.

a. Regulatory Diversity and Uncertainty

Regulatory structures and product classifications vary between the jurisdictions surveyed. The product categories used are similar, though not identical; for example in Australia there is presently no category equivalent to biologics as in the North American regimes. Each jurisdiction has its own definition of common product categories such as drugs or devices and classes within these categories, and while the variation in definitions is not substantial, it raises the possibility that a product may fall within different categories or classes in different jurisdictions. This is especially the case with novel products like stem cell-based products that do not always fit clearly within existing categories, as discussed below. In the context of tissue engineering, it has been observed that “the definition of tissue-engineered products ... is certainly not yet harmonized across the major regulating regions of the world.”¹⁸⁸ The variation among jurisdictions could increase uncertainty and transaction costs for producers and therefore act as a barrier to product development and commercialization.

The regulatory requirements and procedures in all of these jurisdictions are broadly similar, i.e.: product pre-market approval processes requiring submission of data establishing safety, efficacy, and quality; regulation of clinical trials using GCP; regulation and licensing of manufacturing using GMP. This is due in part to the increasing harmonization of therapeutic product regulation under the auspices of the International Conference on Harmonisation (ICH). Remaining differences in the detailed elaboration and application of regulatory requirements will again increase regulatory burdens and costs for producers. This is not a problem unique to stem cell-based products, but it may be exacerbated for novel products such as these because variation among regulatory regimes is likely to be greater. For example, the evolving regulatory regimes on cells, tissues and cell- or tissue-based products differ in their scope of application and, to some extent, in their substantive requirements.

This survey of jurisdictions reveals a clear international trend toward the development and reform of specialized regulatory frameworks to govern cell- and tissue-based products. However, the only jurisdiction that seems to have created specific regulatory categories that are directly relevant to stem cell-based products is the EU, with the new regulation on advanced therapy medicinal products (including gene therapy, somatic cell therapy, and tissue

188 Lloyd-Evans, *supra* note 21 at 49.

engineering). Elsewhere, it remains the case that many prospective biotechnology products, including stem cell-based products, will be regulated according to traditional classifications, despite the fact that they do not fit well into existing product categories and present unique safety, efficacy and quality issues. It has been observed that although existing regulatory regimes “are already in place or can be adapted for some elements of [tissue-engineered products],” most jurisdictions have not adequately addressed these complex products.¹⁸⁹ It has been predicted that “future products will include higher numbers of those which are combinations of drugs and medical devices,” whereas these have traditionally been subject to separate regulations, and that as a result we may need to revisit these categories.¹⁹⁰ The nature of some novel products is such that they may even call into question some of the distinctions used in defining traditional classifications. For example, autologous transplants have traditionally been regulated differently than allogeneic transplants on the assumption that the former carry lesser risks (of infection and immune rejection). However, as Liddell and Wallace have suggested, stem cell-based products raise a question as to “whether cell lines from cloned embryos are to be regarded as autologous ... and whether they are indeed less risky.”¹⁹¹ Therefore, new technologies may require us to reconsider established distinctions and their scientific basis.

Where a product does not clearly fit within single category, there are several possible ways of addressing the situation, each with its own advantages and disadvantages. The categories may be treated as exclusive, so that we must determine which of several potential categories is the best fit.¹⁹² It will therefore be necessary to identify its primary function or characteristics,

189 *Ibid.*, arguing that “only the US Food and Drug Administration (FDA) has grasped the implications of creating and implanting a product that might contain allogeneic living cells, as well as biomaterials and microelectronics.” This assessment would need to be reconsidered in light of the recent developments in the EU.

190 G. Bruce Doern, “Regulatory Regimes for the Safety and Efficacy of Biotechnological Health Products: Changing Pressures, Products and Processes” (2003), online: Canadian Biotechnology Advisory Committee <[http://www.cbac.gc.ca/epic/site/cbac-ccb.nsf/vwapj/Research-2003_Doern-Regulation-Final_e.pdf/\\$FILE/Research-2003_Doern-Regulation-Final_e.pdf](http://www.cbac.gc.ca/epic/site/cbac-ccb.nsf/vwapj/Research-2003_Doern-Regulation-Final_e.pdf/$FILE/Research-2003_Doern-Regulation-Final_e.pdf)> at 9.

191 Liddell & Wallace, *supra* note 1 at 56.

192 This appears to be the approach taken in Australia and Canada to drugs and devices; biologics are a subcategory of drugs in Canada.

in order to determine which product category it is most like: for example, engineered tissue could be a medical device or a drug (or biologic), depending on whether its primary function is as a “support system” or a “vehicle for cells and proteins.”¹⁹³ Regulatory agencies may not necessarily agree with the characterization given to a product by those who develop and market it. One tissue engineering product, used to repair cartilage, was introduced as a medical device, before the USFDA required it to be licensed as a biologic.¹⁹⁴ This type of uncertainty about regulatory classifications and requirements will increase the risks and costs confronting those developing such complex products. It may also mean that the regulatory requirements applied to a product may not adequately address all of its potential risks, because the product classification does not completely capture its relevant characteristics and associated safety, efficacy and quality issues.

Another possible approach is to treat categories as overlapping, so that a product must meet the regulatory requirements associated with all of the categories that may apply. Rather than choosing whether a product is a drug or a device, for example, it could be treated as both and have to comply with the regulations for both categories. This approach has the advantage of recognizing the multifaceted nature of complex products and taking account of the full range of potential safety, efficacy and quality issues. The disadvantage to this approach, however, is that the application of multiple regulatory requirements may introduce delays, increase costs, and act as a barrier to the introduction of novel complex products. As explained above, the United States regime has a specific process and regulatory structure to deal with combination products which fall within more than one category. Although multiple regulatory categories and requirements are applied, the Office of Combination Products is responsible for coordinating review which should, to some degree, reduce delays and uncertainty.

Finally, overlapping or competing categories could be dealt with through a system of priority rules identifying which category's regime will apply if a product falls within two or more categories. This is the approach taken in the new European regulation on advanced therapy medicinal products: if products fall within the definition of both somatic cell therapy medicinal products and tissue engineered products they will be considered tissue engineered products; if they fall within all three categories they will be consid-

193 Lloyd-Evans, *supra* note 21 at 52.

194 *Ibid.*

ered gene therapy medicinal products.¹⁹⁵ This approach may help to address some of the concerns with the other possible approaches, but will only work well where the product categories and associated requirements are designed to ensure that appropriate requirements addressing relevant safety, efficacy and quality issues will apply in each case.

Given that traditional categories of therapeutic products may not be a good fit for stem cell-based products, an argument can be made for the creation of specialized new categories that would be more appropriate. The adoption in Europe of a regulation with requirements tailored to advanced therapy medicinal products is an important step. It recognizes that these are novel, complex products that have unique combinations of characteristics and risks. Determining how the new categories should be defined and what requirements will be adequate is not straightforward, however. As was seen earlier in this article, stem cell-based products are themselves tremendously diverse, though they share certain common characteristics and risks, some of which are also shared by other cell- and tissue-based products. The European approach of regulating specific categories of gene therapy, somatic cell therapy and tissue engineering products, while leaving these products also subject to appropriate aspects of the Tissues and Cells Directive, seems promising and its implementation should be followed with interest.

b. Regulatory Requirements and Their Application to Stem Cell-Based Products

The application of the therapeutic products regulatory regimes to novel stem cell-based products will be challenging for both regulators of these products and those developing and marketing them. Regulatory agencies will need to develop and wisely use specialized expertise in order to adequately assess and monitor the safety, efficacy and quality of stem cell-based products. This will require an investment of human and financial resources, and also suggests that centralization and harmonization will be important to ensuring that regulatory oversight is both adequate and efficient.¹⁹⁶ For example, in the new European advanced therapy medicinal products regulation, centralized authorization of these products was deemed to be appropriate “in order

195 *ATMP Regulation*, *supra* note 150, art. 2(4)-(5).

196 See Doern, *supra* note 190 at 12-14 regarding the need for greater regulatory capacity and international cooperation in relation to biotechnological health products generally.

to overcome the scarcity of Community expertise, ensure a high level of scientific evaluation of these medicinal products in the Community, preserve the confidence of patients and medical professions in the evaluation, and facilitate Community market access for these innovative technologies."¹⁹⁷ The regulation also creates within the European Medicines Agency a Committee for Advanced Therapies with specialized expertise to advise on product evaluations.¹⁹⁸ Other jurisdictions do not have frameworks in place enabling shared or centralized review, but cooperation, information sharing, and harmonization of regulatory requirements can help to achieve some of the same objectives.¹⁹⁹ It has also been suggested that for stem cell-based products and gene therapy, centralized review or registration of clinical trials would be appropriate to deal with the risks inherent in testing these novel products.²⁰⁰

For those developing and marketing products, meeting regulatory requirements may present numerous challenges. Gathering adequate evidence to establish safety and efficacy may be difficult given that "conventional requirements for testing medicinal products may not always be appropriate due to the unique and diverse structural and biological properties" of stem cell-based products.²⁰¹ Another type of challenge is raised in complying with GMP requirements and moving from small-scale laboratory environments to large-scale production in GMP facilities.²⁰² Producers will need to develop methods of standardization and quality control, demonstrate that the products will act as intended *in vivo*, maintain viability of products during storage and transport, and ensure that products remain sterile until administered or transplanted.²⁰³ The three main elements of the manufacturing process

197 *ATMP Regulation*, *supra* note 150, cl. 9.

198 *Ibid.*, cl. 10, art. 8 and ch. 7.

199 See, for example, the work of the ICH on gene therapy: ICH, "Gene Therapy Discussion Group," online: <<http://www.ich.org/cache/compo/276-254-1.html>>.

200 Kimmelman, *supra* note 73; Rosario M. Isasi & Thu Minh Nguyen, "The Rationale for a Registry of Clinical Trials Involving Human Stem Cell Therapies" (2008) 16:2 Health Law Review 56.

201 Tsang, *supra* note 1 at 1974.

202 Polak & Bishop, *supra* note 3 at 360, 362. See also International Consortium of Stem Cell Networks, "International Conference on GMP Issues in Stem Cells" (November 2007), online: North East England Stem Cell Institute <<http://www.nesci.ac.uk/news/events/item/?international-conference-on-gmp-issues-in-stem-cells>>.

203 Polak & Bishop, *ibid.* at 360, 362.

(starting materials, cell populations produced through manipulation, and the finished product) need to be controlled and documented.²⁰⁴ The nature of cell-based products is such that “manufacturing” them is a significantly different process than producing traditional therapeutic products: the material is variable and sensitive, lot sizes may be very small, and the timing of various parts of the process may be critical.²⁰⁵ Long-term measures for surveillance and follow-up may need to be developed in order to address novel safety concerns.²⁰⁶

These differences may make it difficult to meet regulatory requirements in a structure designed to deal with traditional modes of testing and production. The costs of production and regulatory compliance could mean that the price of the eventual product will be unreasonably high or the profit margin unacceptably low,²⁰⁷ clear barriers to commercialization. At present, uncertainty about regulatory requirements and companies’ ability to meet them seems to be acting as a deterrent to investment in cell-based therapies.²⁰⁸

The issues raised here should also be considered in the larger context of ongoing discussions about the reform of therapeutic product regulation. While a full discussion of proposals for reform is clearly beyond the scope of this article, some aspects which have particular relevance for stem cell-based products are worth mentioning here. Questions about capacity may extend to research ethics boards dealing with applications for clinical trials of stem cell-based products, which may lend greater weight to already urgent concerns about the adequacy of Canada’s research ethics review framework.²⁰⁹ Calls for greater public participation in risk assessment and regulation may be seen as especially relevant in the case of stem cell-based products, given the safety concerns associated with them and the ethical issues raised by the

204 Tsang, *supra* note 1 at 1973-74.

205 Preti, *supra* note 40 at 802.

206 Tsang, *supra* note 1 at 1974.

207 Lutz B. Giebel, “Stem Cells – A Hard Sell to Investors” (2005) 23 *Nature Biotechnology* 798 at 799.

208 Wilan, Scott & Herrera, *supra* note 5 at 814-15.

209 See e.g. Michael McDonald *et al.*, *The Governance of Health Research Involving Human Subjects* (Ottawa: Law Commission of Canada, 2000); Paul B. Miller, “Institutional Oversight of Clinical Trials and the Drug Approval Process” (2006) 44 *Osgoode Hall L.J.* 679; Duff R. Waring & Trudo Lemmens, “Integrating Values in Risk Analysis of Biomedical Research: The Case for Regulatory and Law Reform” (2004) 54 *U. of Toronto L.J.* 249.

use of ES cells.²¹⁰ There is also a growing appreciation of the need for more emphasis on post-market surveillance and other mechanisms to address long-term safety and efficacy. Whereas traditional approaches to therapeutic product regulation have relied heavily on the pre-market and approval requirements, it is increasingly recognized that effective regulation requires greater attention to the post-market phase. This would include more stringent and effective post-market surveillance, and possibly other approaches like progressive licensing or conditional marketing approvals.²¹¹ These proposals reflect a broad re-evaluation of our approach to regulating therapeutic products, but they may be of particular importance for biotechnological innovations like stem cell-based products, which have distinct long-term safety issues and a higher degree of uncertainty due to their novelty.²¹²

c. Ethical and Legal Issues

There are numerous ethical and legal issues known to be associated with the use of stem cells. One question to be explored is the extent to which such issues can be (and should be) addressed in the context of product regulation. For example, currently compliance with GCP in clinical trials is required as part of the regulatory framework, and encompasses some legal and ethical requirements such as informed consent of research subjects. In the context of stem cell-based products, there are specific issues relating to the informed consent of the donors of source material. A number of consent issues have been discussed in the context of stem cell research and product development, including informed consent for secondary uses of reproductive material, who should obtain consent for donation of embryos, when and how consent can be withdrawn, and compensation for donors.²¹³ Regulations

210 For discussion of this point see Waring & Lemmens, *ibid.*

211 See e.g. Health Canada, "Planning for Our Future: Federal Regulatory Post-Market Surveillance Strategy 2007-2012" (2007), online:

<http://www.hc-sc.gc.ca/ahc-asc/alt_formats/hpfb-dgpsa/pdf/pubs/strategy_strategie_surveillance_e.pdf>; Health Canada, "The Progressive Licensing Framework: Concept Paper for Discussion" (2007), online:

<http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/proglic_homprog_concept_e.pdf>; Health Canada, "The Use of Post-Market Commitments" (20 September 2007), online: <http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/condition/supra/condition01_e.php>.

<http://26448.vws.magma.ca/dhp-mps/homologation-licensing/docs/condition/supra/condition01_e.php>.

212 Waring & Lemmens, *supra* note 209; Doern, *supra* note 190 at 8-9.

213 See e.g. Timothy Caulfield, Ubaka Ogbogu & Rosario M. Isasi, "Informed

governing cells and tissues within the therapeutic products framework generally deal with donor eligibility, screening and testing, but they do not address consent issues except in a general way.²¹⁴ The consent aspects would therefore be dealt with by other parts of the regulatory context, as explained above, and may be governed by different regulations depending on whether the source is reproductive material (i.e. gametes or embryos) or other cells or tissues.²¹⁵

Another intersection between regulatory frameworks is the possibility of using product approval or licensing requirements as a way of addressing ethical issues relating to the use of embryos. As is well known, countries around the world have taken different positions on the permissibility of research using human embryos and ES cells.²¹⁶ It seems likely, then, that there will also be divergent views on whether products that contain or are created using ES cells should be permitted to be used.²¹⁷ Normally, however, product market-

Consent in Embryonic Stem Cell Research: Are We Following Basic Principles?" (2007) 176 *Canadian Medical Association Journal* 1722; Rosario M. Isasi & Bartha M. Knoppers, "Beyond the Permissibility of Embryonic and Stem Cell Research: Substantive Requirements and Procedural Safeguards" (2006) 21 *Human Reproduction* 2474; Ogbogu, *supra* note 2; George Q. Daley *et al.*, "The ISSCR Guidelines for Human Embryonic Stem Cell Research" (2007) 315 *Science* 603; Marcy Darnovsky & Susan Berke Fogel, "Oocyte Donation for Stem Cell Research" (2007) 316 *Science* 368.

214 See e.g. EC, *Council Directive 2004/23/EC*, *supra* note 145, art. 13 (procurement of cells and tissues only after consent is given in accordance with law in each Member State); *CTO Regulations*, *supra* note 95 (no provisions on donor consent).

215 See *supra* notes 77-81 and accompanying text.

216 See e.g. Rosario M. Isasi & Bartha M. Knoppers, "Mind the Gap: Approaches to Embryonic Stem Cell and Cloning Research in 50 Countries" (2006) 13 *Eur. J. Health L.* 9.

217 Similar concerns may be raised regarding the use of material from chimeras or hybrids. Current regulations may govern the creation and use of these embryos, but not necessarily cover products that are derived from them. For example, it is prohibited under the *AHRA*, *supra* note 77, s. 5 to create a chimera or transplant a chimera into a human being or non-human life form, or to create a hybrid for reproduction or transplant a hybrid into a human being or non-human life form. In the U.K., the Human Fertilisation and Embryology Authority has recently granted a license allowing the creation of a cytoplasmic hybrid embryo for research purposes: Human Fertilisation and Embryology Authority, "HFEA

ing approvals are not based on ethical, social, religious or moral concerns; rather, they depend on evidence-based assessments of the safety, efficacy and quality of the product.²¹⁸ The regulatory frameworks are not designed to consider ethical and social issues, and decision makers would not necessarily have the relevant expertise to do so. The prospect of introducing this element into the approvals process raises concerns similar to those relating to the use of the patent regime to address ethical and social issues, but to an even greater degree. Many patent regimes do already include some limited provision for exclusions based on reasons of morality or public policy (“*ordre public*”), whereas no such provisions currently exist in therapeutic products regulatory frameworks. Although it is theoretically possible for the relevant legislation to be amended, arguably this would be inappropriate for the reasons just described. It would be preferable to address ethical and social concerns separately from product approval, as for example in the European regulatory framework, which treats centralized marketing authorization as separate from national decisions about whether to exclude particular products from sale on moral or ethical grounds.²¹⁹ It remains possible, however, that some will seek to address ethical concerns within the product regulation framework, as for example in proposals that regulators require products containing or derived from ES cells to carry information notifying potential consumers of their origin.²²⁰

Finally, regulatory requirements designed to ensure product safety and quality may themselves raise legal and ethical issues. In products containing live cells, there is “no opportunity for terminal sterilization before delivery,” so “donor eligibility determination serves as a *de facto* safety qualification and entails ... prescreening donors for high-risk behaviors or medical histories that would place the donor at high risk for transmit-

Statement on its Decision Regarding Hybrid Embryos” (5 September 2007), online: <<http://www.hfea.gov.uk/en/1581.html>>.

218 The extent to which this is appropriate, of course, depends on how broadly one defines the risks that should be identified in the product approval process; they could potentially include “risks to social values” which might extend to ethical concerns: see Waring & Lemmens, *supra* note 209.

219 *Supra* note 138, cl. 13; *ATMP Regulation*, *supra* note 150, cl. 7.

220 See e.g. Therapeutic Goods Administration, “TGA Report on Information and Advertising Associated with Products Tested, Created or Manufactured Using Human Embryos or Human Embryonic Stem Cells” (16 September 2003), online: <<http://www.tga.gov.au/advert/stemcells.pdf>>.

ting communicable diseases."²²¹ The extensive donor eligibility screening and testing that may be required to reduce risks of infection and genetic abnormalities will represent a significant intrusion on donors' privacy, and donors will need to be assured of rigorous protection of the relevant information. In addition, samples used in the development of stem cell-based products may potentially be stored for long periods of time. As a result, cells and tissue that are stored must be traceable to allow any safety or quality issues that may arise to be addressed. Systems will need to be in place allowing cells and tissues to be traced back to the donor of the source material.²²² Further testing of samples for infectious agents and markers of genetic diseases may be undertaken as appropriate tests are developed.²²³ The donor's consent to such testing will be needed, either by means of a prospective consent at the time the sample is collected or by tracing and contacting the donor to obtain consent for testing that was not anticipated at the time of collection. These requirements obviously raise further concerns about informed consent and privacy. Donors will need to be informed about traceability provisions and any testing that is contemplated, and measures will need to be taken to ensure, as far as possible, that the data retained for traceability or re-contacting of donors are adequately protected from further disclosure.

Given the novel and heightened safety concerns associated with stem cell-based products, it may also be necessary to provide for traceability of the recipients of these products. For example, the new European regulation on advanced therapy medicinal products requires hospitals or clinics using these products to have systems in place to trace the products and patients who receive them.²²⁴ This will require the collection and updating of sufficient information to allow a patient to be contacted for an indefinite period of time following the treatment. Again, issues regarding both informed consent and protection of privacy will be raised, and the implications should be carefully considered in future research and policy development in this area. Some analogies can be drawn with issues that have been raised and discussed in the contexts of biobanking or tissue banking (with respect to informed con-

221 Preti, *supra* note 40 at 802.

222 See e.g., EC, *Council Directive 2004/23/EC*, *supra* note 145, art. 8.

223 Halme & Kessler, *supra* note 1 at 1731-32.

224 *ATMP Regulation*, *supra* note 150, art. 15(2).

sent, re-contacting and tracing of donors) and xenotransplantation (with respect to traceability and potential restrictions on patient recipients).²²⁵

Conclusion

Along with the technical challenges presented by the development and application of stem cell-based therapies, numerous challenges are associated with their regulation as therapeutic products. Stem cell-based products are very diverse, and carry with them a range of safety, efficacy and quality issues, some of which are distinctive to these products, while others are shared by other cell- and tissue-based products. Given that these products are novel and significantly different from traditional therapeutic products, the regulatory structures by which they will eventually be governed were not designed to accommodate them. This can be seen in the uncertainty and diversity surrounding their classification as different types of therapeutic products in different jurisdictions. Although to some extent this may be inevitable in the case of novel products, it is of concern given that uncertainty may act as a barrier to product development and commercialization, and to associated investment. The uncomfortable fit between novel stem cell-based products and traditional product categories also carries the risk that the regulatory requirements will be inappropriate to adequately address the particular safety, efficacy and quality issues of stem cell-based products – a concern for both product developers and potential patients who will need to be assured that these products are safe and effective.

This review suggests that further work is required in research and policy development to determine the adequacy of current regulatory requirements and the optimal model of regulation for stem cell-based products. There is a clear trend in the jurisdictions surveyed towards specific regulations governing advanced cell- and tissue-based products such as stem cell-based products, with Europe currently leading the way. It will be important to follow

225 See e.g. Bartha Maria Knoppers, "Biobanking: International Norms" (2005) 33:1 J.L. Med. & Ethics 7; J.V. McHale, "Regulating Genetic Databases: Some Legal and Ethical Issues" (2004) 12 Med. L. Rev. 70; Monique A. Spillman & Robert M. Sade, "Clinical Trials of Xenotransplantation: Waiver of the Right to Withdraw from a Clinical Trial Should Be Required" (2007) 35:2 J.L. Med. & Ethics 265; Patrik S. Florencio & Erik D. Ramanathan, "Legal Enforcement of Xenotransplantation Public Health Safeguards" (2004) 32:1 J.L. Med. & Ethics 117.

the development of this regulatory initiative and assess its potential application to other jurisdictions. Finally, as stem cell research moves closer to clinical applications, important work has begun to identify and analyze the associated legal and ethical issues.²²⁶ As this work progresses, it can both inform and be informed by the analysis of legal and ethical issues that arise in the context of therapeutic products regulation. With further development of a responsive regulatory framework, and careful consideration of relevant ethical and legal questions, we can best foster the potential benefits of stem cell-based products.

226 See e.g., Ogbogu, *supra* note 2.