14
Regenerative medicine
Socio-ethical challenges and regulatory approaches

Carla Beak and Rosario Isasi

14.1 Introduction

The advancement of regenerative medicine (RM) has become a popular goal. It is promoted and supported by patients, healthcare providers and governments in an effort to reduce the growing medical and financial challenges in healthcare. This chapter aims to provide a general overview of the ethical, legal and social issues (ELSI) associated with regenerative medicine, beginning by defining the term and briefly summarizing the state of the industry. It discusses issues arising from the use of human cells, challenges of clinical translation, and questions of social justice that emerge from innovations in the field. Lastly, the chapter will turn its focus to the role of the regulatory system in managing the progress and development of regenerative therapies. It will review the ways in which select jurisdictions have adapted existing frameworks to incorporate product development in regenerative medicine, specifically cell-based and combination products, into their regulatory regimes. The chapter then considers elements important to creating a regulatory environment conducive to responsible innovation and international harmonization in RM.

14.1.1 Definition of regenerative medicine

The term regenerative medicine was coined in 1999 to bring the areas of cell transplantation, tissue engineering, stem cells, and nuclear transfer under one umbrella with ‘one unifying concept: the regeneration of living tissues and organs’ (Atala 2009: 575–6). While the field itself is not new, deriving its formal roots early in the twentieth century with studies of regeneration and transplantation (Maienschein 2011), it has experienced resurgence since the derivation of human embryonic stem (ES) cells in 1998 (Shamblott et al. 1998; Thomson et al. 1998) and the creation of induced pluripotent stem (iPS) cells in 2006 (Takahashi and Yamanaka 2006) (see Box 14.1). As such, innovation in RM is an area of interest for scientists, companies and nations aiming to solve healthcare challenges.
There is currently no ‘universally agreed’ upon definition of RM (REMEdiE 2011: 4), due in part to the diverse and interdisciplinary nature of the field. In fact, interdisciplinarity is a key feature of RM, as it integrates expertise from disciplines such as stem cell biology, transplantation, genetics, molecular biology, and tissue engineering (Greenwood et al. 2006: 63). Nonetheless, one commonly used definition proposed by Daar and Greenwood submits that:

Regenerative medicine is an emerging interdisciplinary field of research and clinical applications focused on the repair, replacement or regeneration of cells, tissues or organs to restore impaired function resulting from any cause, including congenital defects, disease, trauma and aging. It uses a combination of several technological approaches that moves it

---

**Box 14.1 Stem cells in RM**

Stem cells (SCs) have an important role in RM research because of their unique therapeutic potential. Stem cells have two key characteristics: (1) they have the capacity to self-renew (make exact copies of themselves) for long periods of time; and (2) they have the ability to differentiate (mature) into other more functional cell types (Lic and Polak 2011: 118). Stem cells can be classified by their differentiation potential – the degree to which they are able to form different mature cell types. ES and iPS cells are pluripotent (they retain the ability to differentiate into cells of the three germ layers: ectoderm, mesoderm, and endoderm). Fetal and perinatal cells are, in general, multipotent (can differentiate into cells of more than one type but not necessarily into all the cells of a given germ layer), whereas adult stem cells are usually oligo- or unipotent (can differentiate into one type of cell only, e.g. muscle or neuron) (Abdulrazzak et al. 2010: S689; Lic and Polak 2011: 118–19). Few adult tissues have been found to have true stem cells. Most can be more appropriately described as progenitor cells, which like stem cells can be multipotent (give rise to several different mature cell lineages) but are not capable of long-term self-renewal (contribute to the maintenance of a tissue for life) (Grompe 2012: 685; Riazi et al. 2009: 59–60).

Research in SC biology has grown considerably across the globe in the past decade (Ben-David et al. 2012: 666). Because of their ability to proliferate and form numerous cell types, there is hope ES and iPS cells can be used in cell-based therapies to cure various diseases. iPS cells in particular are of great interest as they are often considered as a biologically equivalent yet more ethical alternative to ES, although this is a contested assertion (Brown 2009; Hyun 2010: 72–3; Zacharias et al. 2011: 637–8; Kiskinis and Eggan 2010: 52–3; Panopoulos et al. 2011; Puri and Nagy 2012; Robinton and Daley 2012; Yamanaka 2012: 680–1). Unfortunately, the characteristics that make these cells useful also make them technologically difficult to work with and potentially unsafe (Kato et al. 2012: 766; Parker and Perlingeiro 2013: 389). There is still a need for basic research, standardization and validation of the technology before most stem cells can be used therapeutically in RM (Brunt et al. 2012: 330–1; Helmy et al. 2010; Pedersen et al. 2012; Riazi et al. 2009; Sun et al. 2010). As such, many of the SC products and therapies currently making their way through clinical trials use adult stem cells from blood and bone marrow where safety has been better established (Bubela et al. 2012; Daley 2012: 741; Trounson 2009).
beyond traditional transplantation and replacement therapies. These approaches may include, but are not limited to, the use of soluble molecules, gene therapy, stem cell transplantation, tissue engineering and the reprogramming of cell and tissue types.

(Daar and Greenwood 2007: 181)

While a good starting point, there have been questions regarding the scientific accuracy of this broad definition, particularly the inclusion of ‘repair’ as a regenerative process. Thus a more simplified version of the definition was proposed: ‘regenerative medicine replaces or regenerates human cells, tissues or organs, to restore or establish normal function’ (Mason and Dunnill 2008: 3–4). The field is also challenged with questions regarding whether the use of certain technologies and methods should be considered within the scope of RM. While it is common to develop project-specific definitions and boundaries to clearly frame research and analysis, this chapter takes a broad view of the technologies and therapeutic modalities falling within the realm of RM. As summarized previously:

Regenerative medicine deploys small molecule drugs, biologics, medical devices and cell-based therapies.\(^1\) However, the term is more colloquially used to mean advanced therapies based on cells, tissue engineering,\(^2\) developmental and stem cell biology, gene therapy, cellular therapeutics and new biomaterials (scaffolds and matrices).

(Department for Business Innovation and Skills (BIS) 2011: 6)

14.1.2 RM industry

Several efforts have been made to gauge how the field of RM is progressing as an industry (Ginty et al. 2011; Jaklenec et al. 2012; Lewis 2013; Mason et al. 2011) and what this means for health care (Kessler 2007; Parenteau et al. 2012; Prescott 2011). As would be expected due to the diverse nature of RM, these studies find that the field is developing on different fronts and over a range of activities. Markers such as revenue, clinical trials in progress, and patent activity demonstrate the industry’s positive trajectory. Currently, however, a scarcity of market products indicates that product development driven by medical need, technological feasibility, and affordability should be a priority. Additionally, scientific progress in the field has been promising (Atala 2012; Fisher and Mauck 2013; Horch et al. 2012), which has generated both hope and hype for the industry (Brunt et al. 2012: 328). Yet, it has been noted:

A brief review in the recent bibliography concerning advances in TE and [RM] would raise the impression that ‘we are almost there’ … Interestingly enough, that was exactly the spirit

---

\(^1\) A central focus of RM research and translation efforts are in the cell therapy, using a variety of cell types and approaches (Culme-Seymour et al. 2012). While cell therapy with stem cells from bone marrow for the treatment of hematopoietic diseases has been in use clinically for more than 50 years, it is probably the only safe and controlled stem cell-based therapy routinely used today (Ilic and Polak 2011: 124). Essentially all other stem cell treatments remain experimental (Daley 2012: 740).

\(^2\) Tissue engineering (TE) is defined as the use of a combination of cells, engineering, materials, and methods to manufacture ex vivo living tissues and organs that can be implanted to improve or replace biological functions, usually through the use of scaffolds for restoration or regeneration of tissues or organs (British Standards Institution (BSI) 2012b: 883). While some reports use the terms TE and RM interchangeably (Jaklenec et al. 2012: 155), others consider RM a superordinate concept (Horch et al. 2012: 1158), and others bring the concepts together – TERM – capturing the broad nature of the field (Fisher and Mauck, 2013: 1).
some 10 years ago … An ever perpetuating evolution is yet to bring the long awaited revo-
lution in the health sector.

(Polykandriotis et al. 2010: 2351)

So while there are great hopes for RM, only time will tell which products and strategies will be clinically useful and translate into healthcare practice. This progress may take decades if the field follows the historical pattern of gradual technological change, and will require the development of complementary technologies, organizational innovation, and new forms of governance (Hopkins et al. 2007: 585). Moreover, the policies that accompany this process will require thoughtful consideration of ELSI.

14.2 Legal and ethical issues

14.2.1 ELSI in RM

Before detailing some of the principal socio-ethical concerns relevant to RM, it is important to highlight two general issues that permeate ELSI considerations. First, from a technological standpoint, RM does not present new ethical issues to those seen in other research areas (such as cell biology, genetics and genomics, transplantation and reproductive research). Rather, the complexity and variability of products and processes used in RM enhances the level of risk to patients, which increases the breadth and degree of ethical issues and raises the level of concern compared to other products (Lowenthal et al. 2012: 409; Trommelmans et al. 2009: 464). There are three main features of RM products that lead to this higher level of risk: (1) they show a certain amount of variability because they contain metabolically active cells in a dynamic extracellular environment; (2) they are intended to integrate, interact, and evolve with the body to achieve regeneration of the tissue; and (3) because of this interaction, the process of regeneration is impossible to fully reverse once started – the product itself can be removed, but the influence of cells or biomolecules on surrounding tissues cannot be undone (Oerlemans et al. 2013: 43–4).

Second, from a social standpoint, it may be difficult to ensure stakeholders are aligned in the development and application of socio-ethical, legal, and regulatory requirements for RM product research and development. Researchers (primarily biologists and biomaterial specialists) may have limited familiarity with ethical issues, and ethicists may be unfamiliar with the complexity of RM science and its ethical considerations (Trommelmans 2010: 24). Product developers are predominantly academics and small to medium-sized enterprises (SMEs) who may lack the development resources and experience of Big Pharma (Ginty et al. 2011: 242; Lewis 2013: 19, 23–9). Regulators have limited experience with RM technologies and products, so they may be conservative in their regulatory approach (McAllister et al. 2012: 94; Messenger and Tomlins 2011: H11). Insurers are tasked with ensuring social interests (value for money and meaningful health outcomes) are considered before incorporating RM products into public health systems (Jensen and Jacques 2011; Warren 2013). The public has been a powerful lobbying force for technological development, but is quite uninformed regarding nuanced ELSI considerations (Bubela et al. 2012). Furthermore, all of this is taking place globally in contexts ‘where Western ethical sensitivities are not always the prime concern’ (Trommelmans 2010: 24), and where legal and regulatory frameworks may not exist or be enforced. Thus within this context, three main areas of ELSI consideration are presented: the use of human cells; clinical translation; and social justice in innovation.
14.2.1.1 Use of human cells and tissues

The public is familiar with the unresolved socio-ethical, legal, and political debates around the use of stem cells (International Stem Cell Forum Ethics Working Party (ISCF-EWP) 2006), particularly with regard to the derivation of stem cells from embryonic sources (Isasi and Knoppers 2009a), but which now have expanded to include other cells like iPS (Hyun 2010; Zarzeczny et al. 2009). While the socio-ethical arguments remain unsettled in some jurisdictions (Isasi 2009a; Isasi and Knoppers 2006), the science continues to progress, and legislation and professional guidelines have been developed to steer the field. Some guidelines address areas like banking and databases, covering issues of governance (ethics and scientific review, oversight, etc.), protection of and access to samples and data, and benefit sharing and disposal policies (International Stem Cell Banking Initiative (ISCBI) 2009; ISCF-EWP 2012; The Organization for Economic Cooperation and Development (OECD) 2009). Other guidelines address human stem cell research and speak to areas like ethical research practices, obtaining informed consent from donors/subjects, and mechanisms for the oversight of research (International Society for Stem Cell Research (ISSCR) 2006).

In application, however, there is still a host of issues that need to be considered. There are issues that need to be addressed when considering public versus private banking systems (such as exploitation and equity) (European Science Foundation (ESF) 2010: 8), clinical versus research banks (such as access, standardization, and public investment) (Ilic and Stephenson 2013; Isasi and Knoppers 2009b) and data transfer and sharing systems (incentives, privacy, ownership) (Kato et al. 2012: 765–6; Trommelmans 2010: 25). Of particular concern are inconsistencies and challenges in the area of informed consent. For example, in ES cell research, issues regarding gamete and embryo donor rights and conflict of interests at recruitment warrant examination (Cohen and Majumder 2009: 83–90; Lo et al. 2010). Regardless of sample source, obligations regarding confidentiality, traceability, return of results and benefits, withdrawal of samples, sample storage and exchange are salient ethical issues for policymaking – to name a few (ISCF-EWP 2012; Isasi et al. 2011; Knoppers and Isasi 2010; Lowenthal et al. 2012).

14.2.1.2 Clinical translation

There are many international and national codes and guidelines that address the ethics of research involving human subjects (Office for Human Research Protections 2013). They cover issues ranging from ethics review, oversight, informed consent (at the community, family, and individual levels), subject rights, and scientific standards. In 2008, the ISSCR adopted a best practice guideline entitled Guidelines for the Clinical Translation of Stem Cells (Guidelines). The Guidelines address cell processing and manufacture, preclinical studies, and clinical research with the aim to ensure ‘that basic stem cell research is responsibly translated into appropriate clinical applications for treating patients’ (ISSCR 2008: 2). But perhaps before considering effective strategies for translation, the first question should be whether RM technology is ready for clinical translation at all. Many commentators fear experimental RM therapies are entering the clinic without the basic scientific information needed to assess mechanism of action, determine risk of side effects (safety), or establish standard processes for assessing quality and functionality (efficacy). This ‘hyperacceleration’ of translation is not unfamiliar to biotechnology; it is often associated with conflicts of interest, and as such can have a significant impact on human subjects as well as public trust (Wilson 2009).

The presence of strong preclinical research is a necessity for clinical translation. Currently in RM, there are limits to the utility of preclinical data, in part due to the relevance of animal
models (Henderson et al. 2013; Kato et al. 2012: 765; Trommelmans et al. 2009: 463). This has led to an increase in the use of first-in-human (FIH) experiments in early clinical research to determine safety and efficacy, which raises a number of ethical issues (Chapman and Scala 2012). In these early stage trials, important questions arise regarding patient recruitment (disease stage, pay-to-participate) and the use of appropriate outcome measures and controls (standard of care, sham surgeries) (Ginty et al. 2011: 247; Kato et al. 2012: 766; Niemansburg et al. 2013: 68–70; Sipp 2012). These aforementioned issues feed broader ones regarding the evaluation of risks and benefits, and how this impacts the informed consent process.

A favourable risk : benefit ratio is an important ethical requirement in clinical research (Niemansburg et al. 2013: 65–7). For many RM products, performing a definitive risk-benefit analysis is difficult since the products are novel and complex. It is challenging to compare these interventions to existing standards of care, and patient responses will vary depending on factors such as disease stage. Combine this with the prevalence of therapeutic misconception – the false belief in the clinical benefit of an experimental procedure – and obtaining genuine informed consent from participants becomes a significant challenge (Trommelmans 2010: 25). Considerations must also be made for vulnerable populations, as discussed in Chapters 5–7. Because of their long lifespan post treatment and the use of proxy consent, there are different ethical implications for research on children, which changes the risks tolerated and the procedures considered suitable for child participation (Oerlemans et al. 2013: 44). Even more concerning is consent for the use of experimental cell therapies in clinical situations where basic scientific evidence has not been obtained, where standard research protocols are not followed, and where regulatory and safety guidelines are not met (Bianco et al. 2013). This is a trend seen in the growing medical tourism industry, a topic discussed in Chapter 24.

14.2.1.3 Social justice in innovation

RM is a global industry, and many governments are investing in RM innovations. Therefore, it would be ill advised to ignore the broader social issues and implications of investment in this area. RM technologies raise a number of social justice-related questions. Who will benefit from the therapies that are developed? Will the therapies be suitable for use in the entire population (Giacomini et al. 2007)? As these new therapies are expected to be expensive, who should get access to them (Trommelmans 2010: 25)? Will the nations that dedicated time and resources in research be the ones to access and benefit from therapies once commercialized (ESF 2010: 10)? Is it appropriate to use RM technologies in the prevention of aging or in cosmetic enhancement (Trommelmans 2010: 25)? The ISSCR, Guidelines for Clinical Translation of Stem Cells highlight the importance of public engagement in its discussion of social justice considerations, which includes recommendations on the reporting of results, genetic diversity in cells used, and fair access to therapies developed in both resource rich and poor countries (ISSCR 2008: 16–17). The issue of access is discussed in Chapter 22.

These discussions relate to those regarding the social objective of innovation and the repercussions of private commercialization of publicly funded national research (Caulfield et al. 2012; Regenberg and Mathews 2011). Considering that public support, financially and politically, continues to drive RM innovation, it is especially important that the public be aware of the implications of the research. It has also been noted that fiscal, regulatory, and scientific issues are absent from media reports and hidden from public discourse (Bubela et al. 2012). The cost of RM therapies is expected to be high, requiring a significant health payoff to justify its use (Giacomini et al. 2007: 1499). While RM will no doubt provide new and superior therapies for any number of indications, many commentators are doubtful of the anticipated savings the
healthcare system will witness given the costs and high bar for therapeutic value of RM research. In addition, governments need to assess the value of investment in RM innovation in relation to other health care approaches (Trommelmans 2010: 25). It should be considered that the economic benefit of RM may not materialize, and that using it as a justification for public funding may have unintended consequences (Caulfield 2010; Hopkins et al. 2007: 585–6).

14.2.2 Regulation of RM

While RM innovations promise improvements in individual and population health, there is a need to balance enthusiasm and investment with attention to resource distribution and safety. It is in determining this balance that regulations play a role, helping to direct product development and ensure safety and efficacy. Alongside governmental hopes that RM will reduce healthcare costs and stimulate economies (Alberro 2012: 605; BIS 2011: 3), there is a concern that RM products pose challenges to existing regulatory systems (Bravery 2010: S789). As we have discussed, RM can incorporate a combination of drugs, medical devices, and/or cell therapies. The complexity and novelty of these products make them difficult to classify for regulatory purposes and stretch the limits of our existing knowledge about how to assess their safety and efficacy (von Tigerstrom 2011: 84). The regulatory process is only one element in a complex network of biomedical research governance that includes institutions, systems, collaborations, and economical and reputational pressures (BIONET 2010a: 42). As we learned from the attempted translation of gene therapy technologies, however, preclinical and clinical regulation of novel therapies is a key lever in steering the new industry (Wilson 2009: 324). Moving forward without effective regulation not only puts patient safety at risk, but also undermines the social trust and support in RM that has been pivotal to its development.

14.2.2.1 Role of regulations

The primary role of regulation is to ensure new products and therapies are safe and effective. In the research setting, scientists and clinicians regard laws and regulations as an essential part of any ethical framework in biomedical research (BIONET 2010a: 13). Consequently, since RM is a global endeavour, regulatory coherence, regulatory gaps, and implementation of ethical standards on the ground are important considerations for multinational research collaborations (BIONET 2010b: 41–3). In the context of commercialization, experience in medical innovation has shown that clear and effective regulations are an essential facilitator of progress in this process (Messenger and Tomlins 2011: H11). Regulatory agencies play a central role in controlling the structure, cost, and approach of the regulatory system, which in turn influence the companies and products entering the market (Tait et al. 2007: 7–8). Regulations will change and adapt as the science advances, and as researchers and regulators learn more about the properties of novel therapies. However, it is the regulatory system and clinical trial process that ensure public safety during this time of scientific advancement (Werner et al. 2012: 103).

14.2.2.2 Challenges with regulations

Despite its vital role, the regulatory system has faced its share of challenges in the RM field. The diversity of stakeholders (each with their own interests) makes it difficult to cultivate an ongoing dialogue with regulators, which makes policy development challenging (Whittlesey and Witten 2012: 595). A legitimate lack of knowledge and experience with RM products hinders the
establishment of standard regulatory requirements, and regulators are required to review applications on a case-by-case basis (BIS 2011: 47). In turn, product developers, at times under direction from inexperienced regulators, can waste time collecting the wrong data for regulatory submissions (Plagnol et al. 2009: 554). In addition, there are concerns that regulatory systems give multinational companies a dominant role over innovation in healthcare through lengthy, expensive, and complex regulatory requirements that stifle new entrants and innovations (Tait et al. 2007: 29–30). Even countries with mature regulatory regimes struggle to maintain an efficient regulatory system for RM-related products. A recent report by the UK House of Lords Science and Technology Committee, which focused on the translation and commercialization of RM research, found ‘[t]he twin challenges of improving perceptions of the regulatory system and streamlining it are so great that both immediate and long-term action are needed’ (House of Lords 2013: 42).

14.2.2.3 Importance of product classification

Classification is an essential consideration in regulating new products. The type of product or therapeutic approach selected during product development impacts what regulatory category applies and, in turn, the regulatory requirements that must be adhered to. Because classification dictates the scientific evidence required, it is important for researchers to be able to predict classification decisions with some certainty (von Tigerstrom et al. 2012: 626). In fact, it has been recommended that RM product developers allow regulations to drive the innovation process in an effort to avoid regulatory burdens down the road (Ginty et al. 2011: 245). Unfortunately, many RM products at this stage are unique and definitions and product classifications are ‘not yet settled’ (Harmon et al. 2011: 2). Product classification has a significant effect on the degree of efficacy and safety that must be demonstrated before the product can be approved for patient use, and hence impacts development time and costs (Messenger and Tomlins 2011: H12). As such, it is on the product classification front that many of the regulatory and legal battles over RM technologies and their uses are occurring (see Boxes 14.2 and 14.3).

14.2.2.4 Importance of standards and harmonization

While product classification is important for the regulatory path, the technical standards used to evaluate RM products will dictate the difficulty in navigating this path. If clear standards (addressing specifications, methods, practices and/or definitions) are in place, a product’s variability will be minimized and its safety will improve. Standard setting regulations and guidelines require that scientifically established norms and requirements (i.e. standards) be followed. Examples include Current Good Manufacturing Practice (CGMP) and Current Good Tissue Practice (CGTP). An Ernst & Young review concluded there was a significant, yet often unrecognized, role for standards in creating and developing emerging technologies (BIS 2011: 35).

Unfortunately, RM will prove a difficult field in which to establish standards. A therapy that uses living cells cannot be standardized in the same way as a conventional pill: different quality and safety requirements are needed (Duffy 2011). Although standardization is generally useful in alleviating uncertainty, there is also a risk that efforts to adopt uniform standards will raise the regulatory bar ‘too high’ (von Tigerstrom et al. 2012: 627). Research also indicates that it is difficult to establish the proper infrastructure to meet regulatory requirements, especially for investigators from educational institutions. Compliance with quality standards such as CGMP is onerous and costly, and thus necessitates sufficient funding to meet these standards (von Tigerstrom et al. 2012: 627).
Box 14.2 National challenges to EU regulation: the Stamina Foundation

As described by Bianco *et al*., the Stamina Foundation in Italy performs what it calls a novel proprietary method of mesenchymal SC (MSC) in vitro isolation and differentiation into neurons, for which there is no retrievable scientifically published account (patent applications have been submitted in the US and European patent offices under the names of Foundation members). The cell preparation is then injected into patients to treat a range of neurological diseases including lysosomal storage diseases, Parkinson’s disease and other kinds of irreversible brain or spinal damage. Treatments were taking place in collaboration with a public hospital. From a regulatory perspective, the treatment was intended for ‘compassionate use,’ defined as a treatment unapproved, but tested as safe, and with preliminary evidence of potential efficacy in the absence of a sound therapeutic alternative to treat a single case outside of a formal clinical trial. The EMA has deferred to member countries for specific regulations regarding its use (*Regulation* (EC) No. 1394/2007, article 28). In 2006, the Italian government issued rules intended to provide guidance in these cases. However, the rules were insufficient, creating room for unauthorized and unproven treatments. Multiple violations were detected by the Italian regulatory body, the Italian Medicines Agency (AIFA), which ordered the practice to be stopped in 2012. In addition, testing of a vial of cells (that were to be infused into patients) following an inspection of the Stamina laboratory in Brescia found that the claims for the cell identity, purity, and properties could not be supported (Bianco *et al*., 2013: 2–3).

The shut-down of the Foundation’s activities led to mass public outcry and lawsuits by patients and families. Multiple courts ruled in favor of the patients and ordered the hospital to resume treatments in spite of the AIFA ban. The Italian government was then forced to issue *ad hoc* regulatory measures. Under Senate debate, regulations and good manufacturing practice (GMP) requirements intended to apply were cancelled, and instead they proposed equating stem cell therapies with direct transplantation of tissues and cells. This would cancel their definition as ‘medicines’ and thus exempt them from AIFA and EMA regulation and oversight (Bianco *et al*., 2013: 2). This signalled a striking departure in policy which stunned the scientific community, who considered the Stamina Foundation’s therapy highly questionable and feared the lack of regulatory oversight would hurt patient safety and undermine the credibility of the cell therapy field (Margottini 2013a). In the end, cooler heads prevailed and stem cell therapies will remain regulated as advanced therapies. While Stamina continued to treat patients already undergoing the therapy, it could not accept new patients. However, the new bill also set aside €3 million for a clinical trial of the Stamina treatment, a large sum considering stem cell research last received national support in 2009 – to the amount of €8 million (Margottini 2013a). The clinical trial was to be led by AIFA, the Italian National Health Institute, and the National Italian Transplant Centre, be designed by a scientific board, and follow rules set out by the EMA and AIFA under *Regulation* (EC) No. 1394/2007. These requirements included using cells manufactured according to GMP, which Stamina’s director claimed would hamper the efficacy of the treatment (EuroStemCell 2013; Margottini 2013a). Additional issues quickly emerged as evidence surfaced that the method’s patent application contained falsified data and the Foundation postponed commitments to reveal the methodology to the trial design committee (Abbott 2013). Ultimately the committee rejected the method for use in a clinical trial. With the Ministry of Health announcing that a clinical trial will not take place, the fate of patients currently undergoing treatment is uncertain (Margottini 2013b).
Box 14.3 Challenge to FDA authority: Regenerative Sciences

The most notable legal challenge to the regulatory power of the FDA in RM, specifically cell therapy, is that of Regenerative Sciences Inc. of Colorado. This ongoing legal battle began in 2008 when the FDA sent the Medical Director of Regenerative Sciences a letter stating that, based on information obtained on the company website, the FDA had determined the company was promoting the use of MSCs as biological drugs (under section 201(g) of the Federal Food, Drug and Cosmetic Act 1938 (FD&C Act) and section 351(i) of the Public Health Service Act 1944 (PHS Act)), and, as such, it falls under FDA regulation. The procedure (Regenexx™) involves removing the patient’s bone marrow, which is then sent to a lab, isolated and then grown and expanded using growth factors drawn from the patient’s blood. The cells are then injected into the patient to regenerate bone and cartilage for the repair of orthopedic conditions. The FDA claimed that as the cells are intended for the cure and treatment of disease in man, they can be considered a biological drug. Therefore an Investigational New Drug Application is required for clinical use in humans, and a Biological Licence Application, which reveals the safety and efficacy for the intended use, is required for interstate commerce. The human cells, tissues, and cellular- and tissue-based products (HCT/Ps) in question did not meet the requirements for exclusion from the licensure requirements (21 CFR 1271.10). Therefore, the firm was found in violation of the Acts (Malarkey 2008).

This letter was followed up by multiple inspections in 2009 and 2010 which found that the laboratory in question did not operate in conformity with CGMP. Regenerative Sciences then filed a complaint against the FDA claiming it did not have jurisdiction to regulate the homologous use of stem cells. After a series of decisions and motions in 2010 and 2011, the most recent ruling came on 23 July 2012 in US v. Regenerative Sciences, LLC et al. (2012) 878 F. Supp. 2d 248. The question presented was whether the Regenexx™ procedure constituted a biological drug subject to FDA regulation or whether it is merely an intrastate method of medical practice subject only to the laws of the State of Colorado. The FDA asserted that the Regenexx™ procedure constituted the manufacturing, holding for sale, and distribution of an unapproved biological drug product, and that Regenerative Sciences had also violated the FD&C Act’s prohibition on adulteration and misbranding a drug. Regenerative Sciences argued that the Regenexx™ procedure constitutes the practice of medicine as defined by Colorado law and that the FDA lacks jurisdiction to regulate it. In addition, it claimed that the procedures occur entirely intrastate and is not covered by the Commerce Clause or the FD&C Act, which limit federal power to interstate commerce. The court found in favor of the FDA on all counts, and dismissed Regenerative Sciences’ eight counterclaims. While Regenerative Sciences agreed to stop using the Regenexx™ procedure pending the lawsuit, the court believed there to be a ‘cognizable danger of recurrent violation’ and granted the FDA’s request for a permanent injunction (US v. Regenerative Sciences, LLC et al.). Officials from Regenerative Sciences have said they plan to appeal the ruling (Swinderman 2012). However, commentators have noted that ‘the rules of statutory interpretation and administrative procedure will weigh in the agency’s favor in this case, especially with this particular set of facts’ (Chirba and Noble 2013: 4). They also noted that suing an agency is often a losing battle, and question whether such cases will do much to lower regulatory hurdles (Chirba and Noble 2013).
During the past decade, regulatory frameworks and the development of standards have improved, and this will facilitate commercialization (Messenger and Tomlins 2011: H16). It is important to note that national standards are of limited value in a global enterprise such as RM: standards must be agreed upon at the international level in order to maximize their utility. Harmonizing international policy, therefore, is especially important in RM where standardization of processes and products is not always attainable. Harmonization – the adjustment of inconsistencies among different procedures or systems to make them uniform or mutually compatible – can range from informal cooperation to the development of common technical requirements (von Tigerstrom 2008: 657).

14.3 Regulatory approaches

14.3.1 Regulatory frameworks

Several jurisdictions have begun the process of updating their regulatory systems to integrate increasingly novel and complex technologies like RM, which do not fit into existing frameworks designed for pharmaceuticals and medical devices. In particular, the European Union (EU) and the United States (US) developed new governing bodies with the relevant expertise, and regulations to establish new product categories, which are a starting place for the regulation of RM products. Other jurisdictions, such as Canada, to date have relied on a more informal approach (via policies) to manage RM products through existing regulations. Tables 14.1 to 14.3 (pages 256–261) offer a brief overview of the regulatory systems in the EU, the US, and Canada, focusing primarily on the regulatory approach required for cell-based RM therapies that may consist of other components (i.e. are combination products). In particular, the regulations highlight product classification, standards for the use of cells and tissues, requirements for clinical testing, manufacturing practices, authorization for sale, and product surveillance.

14.3.2 Summary: potential for harmonization

This tabular description of each country’s regulatory system is by no means exhaustive. It omits many details, such as labeling, and areas that are relevant to a variety of RM products, such as the use of medical devices. However, it does illustrate how different jurisdictions have adapted their regulatory systems to the new, complex products emerging in RM. In particular, it allows us to identify the similarities and differences in regulatory approaches, as well as their weaknesses and strengths. Fortunately, there is general agreement among the three jurisdictions with regard to the regulatory approaches used. In fact, an analytical report issued by the Tissue Engineering and Regenerative Medicine International Society (TERMIS) identified six similarities between the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approaches (which also apply to the Canadian context). They:

1. Adopt a risk based/tiered approach to evaluate specific risks unique to each submission.
2. Identify specific pathways for therapies to reach market quickly if they are safe and effective.
3. Promote long-term follow up on safety, efficacy, and durability of products and outcomes.
4. Enter into agreements for parallel advice and collaborations with industrial organizations on the regulation of product development and conduct joint reviews.
5. Encourage sponsors to meet so agencies can offer specific guidance to sponsors in key technological areas of concern.
6. Accept international studies for marketing applications if they meet specific requirements for data validity, GCP, and appropriate supporting information.

(Bertram et al. 2013: 192)

While most commentators have been in favor of the EMA’s approach to the regulation of these complex products, implementation will dictate whether the regulations are effective in protecting the public while encouraging innovation. Indeed, differences in implementation at the national level could undermine the establishment of safety and effectiveness standards. For example, each member state will have different ethics committees, ethical viewpoints, and oversight mechanisms, which may impact how clinical trials are performed (Ginty et al. 2011: 247). In addition, the potential for legal maneuvering at the national level could compromise regional regulatory efforts (see Box 14.2). However, the EU regulatory approach offers great potential in setting an example for harmonization — creating overarching standards while respecting national interests. By having a centralized regulatory approach, the US has the potential to offer a more consistent regulatory regime, although concerns have arisen regarding the effectiveness of the Primary Mode of Action approach to regulating combination products.

As a dominant force in both RM research and commercialization, the US has the privilege of being able to set its own regulatory path, independent of other jurisdictions. Nonetheless, perhaps more than any other jurisdiction, the FDA faces legal challenges to its authority (see Box 14.3). Considering the global nature of RM, the impact of its regulatory approach in and outside of US borders should be considered. This could influence countries like Canada, which to date has had limited regulatory guidance for RM products. Instead, regulators are guided by policy addressing areas such as combination products, which is interpreted and implemented on a case-by-case basis. While individual case analysis provides regulators with the flexibility required to manage the unique needs of each product, it also allows for potential arbitrary applications or inconsistencies, and leaves researchers and product developers with little guidance or certainty. Lastly, it is especially important for smaller jurisdictions like Canada to ensure its regulatory system is harmonized with those of larger entities like the EU and the US to fully participate in the RM field. Harmonization is thus a stated goal in the Canadian regulatory modernization efforts, and an important area of discussion in developing countries as well (Viswanathan et al. 2013).

14.4 Emerging issues

14.4.1 Moving forward on the regulatory front

Balancing clarity and consistency with flexibility is a particular challenge for regulators, as this balance is essential to facilitate the emergence of a new and evolving field. Communication is often cited as the key to addressing the challenges regulatory bodies face in establishing clear, harmonized regulatory frameworks with standards that are responsive to the changing needs of the industry. To ensure quality, safety and efficacy of novel products and therapies, regulators must develop an understanding of the scientific issues at hand, and rely on early contact with industry to address matters of product classification, scientific uncertainty, and product certification (Harmon et al. 2011: 3). They must work with scientists to frame safety guidelines based on acceptable risk, and promote involvement and communication from standard-setting organizations, health authorities, production, and preclinical testing specialists (Goldring et al. 2011: 626). For these collaborations to occur, a regulatory agency must have adequate resources and
Introduction

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications for market authorization of new products via the EU’s centralized procedure. The EU has created a new product category, Advanced Therapy Medicinal Products (ATMPs), and an expert committee, the Committee for Advanced Therapies (CAT), specifically to manage the complex products entering the regulatory system from the RM field. The associated regulations (Regulation (EC) No. 1394/2007) outline market authorization procedures and requirements specific to ATMPs, referencing additional regulations as they apply.


Regulation (EC) No. 1394/2007 lays down the specific rules concerning the authorization, supervision and pharmaco-vigilance of ATMPs. ATMPs (defined as a gene therapy medicinal product, somatic cell therapy medicinal product, or tissue engineered product) are biological medicinal products (any substance presenting as having properties for treating or preventing disease, produced or extracted from a biological source) as defined under Directive 2001/83/EC (Annex I). However, because of the novelty, complexity and technical specificity of ATMPs, specially tailored and harmonised rules were needed.

Regulation (EC) No. 1394/2007 states that, due to the complexity of combined ATMPs containing viable cells or tissues, whatever the role of the medical device, the pharmacological, immunological, or metabolic action of these cells or tissues should be considered to be the principal mode of action of the combination product. Such combination products should always be regulated under this Regulation.

Article 3 states where an ATMP contains human cells or tissues, the donation, procurement, and testing of those cells or tissues shall be in accordance with Directive 2004/23/EC. It requires member states to put in place a quality system based on the principles of good practice.

Clinical trials on ATMPs should be conducted in accordance with principles and ethical requirements laid down by Directive 2001/20/EC and Commission Directive 2005/28/EC, which, for example, require member states to establish Ethics Committees and observe good clinical practice. Article 4 of Regulation (EC) No. 1394/2007 states the Commission shall draw up guidelines on good clinical practice specific to ATMPs.

Supplemental Regulations:

2001/83/EC: community code relating to medicinal products for human use. It requires an application for a market authorization, which is to be issued before a medicinal product may be placed on the market.

Annex I: analytical, pharmaco-toxicological, and clinical standards and protocols in respect of the testing of medicinal products (replaced by 2003/63/EC). It details the requirements for the Marketing Authorization application dossier.

2004/23/EC: on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human cells.

2001/20/EC: on the approximation of the laws, regulations, and administrative provisions of the member states relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.
Manufacturers of ATMPs should be in compliance with the principles of good manufacturing practice as set out in the Commission Directive 2003/94/EC, and adapted where necessary to reflect the specific nature of those products. Article 5 of Regulation (EC) No. 1394/2007 states the Commission shall draw up guidelines in line with the principles of good manufacturing practice and specific to ATMPs.

The centralized authorization procedure, as laid down in Regulation (EC) No. 726/2004, is compulsory for ATMPs. It outlines the application procedures and requirements (such as the submission of preclinical and clinical data) to obtain market authorization from the European Commission. The opinion is drawn up by the Committee for Medical Products for Human Use under guidance from CAT. The application shall be refused if the quality, safety or efficacy of the product has not been demonstrated. Marketing authority cannot be granted by individual member states. Article 9 of Regulation (EC) No. 1394/2007 states where a combined ATMP is concerned, the whole product shall be subject to final evaluation by the EMA.

Article 14 states that in addition to requirements for pharmacovigilance described in Regulation (EC) No. 726/2004, the applicant shall detail the measures envisaged to ensure the follow-up of efficacy of ATMPs and adverse reactions. Where there is particular cause for concern, a risk management system must be set up or specific post-marketing studies be carried out.

Article 15 states that the holder of a marketing authorization shall establish a system of ensuring that the individual product and its starting and raw materials can be traced. The hospital, institution or private practice where the ATMP is used shall establish a system for patient and product traceability.

Table 14.2 Regulation of RM products in the US: human cells, tissues, and cellular and tissue-based products

**Introduction**

The Food and Drug Administration (FDA) is the centralized department mandated with regulating therapeutic products in the US, including licensing for clinical trials and market authorization. It executes its mandate via three departments of relevance to RM products: the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), and the Center for Devices and Radiological Health (CDRH). To manage issues that have arisen in the development of new RM technologies, the regulatory category of human cells, tissues, and cellular and tissue-based products (HCT/Ps) was created (21 CFR 1271). In addition, regulation was implemented to guide management of combination products (21 CFR 3). The Office of Combination Products (OCP) was created to develop guidance and help determine which center should lead the regulation, based on the products’ primary mode of action (PMOA).

**Title 21 Code of Federal Regulations Part 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products (21 CFR 1271)**

21 CFR 1271 determines the applicable regulatory regime for cell therapy products and requires the registration of HCT/Ps (articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient). It distinguishes between HCT/Ps regulated under section 351 of the Public Health Service Act 1944 (PHS Act) and section 361 of the PHS Act. To be regulated solely under section 361, a product must (1) be minimally manipulated, (2) be intended for homologous use, (3) not combine cells with another non-exempted article, and (4) not have a systemic effect or be dependent on the metabolic activity of living cells for its primary function (excluding exemptions).

As cell-based RM products would typically not meet these criteria, they are generally regulated under section 351 of the PHS Act. In addition to all other applicable regulations, section 351 PHS Act products must register with the FDA, submit a list of HCT/Ps manufactured, and comply with subparts B (procedures for registration and listing), C (donor eligibility: screening and testing), and D (Current Good Tissue Practice: to prevent introduction, transmission or spread of communicable diseases) of 21 CFR 1271.

**Supplemental Regulations:**

42 USC 262 (351 PHS Act): Regulation of Biological Products. Defines biological product and requires a licence for their sale. It also outlines labeling, inspection, and recall rights and penalties for non-conformity.

42 USC 264 (361 PHS Act): Regulations to Control Communicable Diseases. Authorizes the Surgeon General to make and enforce regulations to prevent the introduction, transmission, or spread of communicable disease.

For a 351 PHS Act product, 21 CFR 58 applies: Good Laboratory Practice for Nonclinical Laboratory Studies.

**Title 21 Code of Federal Regulations Part 3 Product Jurisdiction (21 CFR 3)**

For combination products, 21 CFR 3 also applies. This implements section 503(g) of the Food, Drug, and Cosmetic Act (FD&C Act) 1938. Because of the complexity of the products, there is no single development paradigm for combination products. Three potential product categories are recognized:

- **Drugs:** Regulated by 21 CFR parts 200–299, 300–369 under CDER, requires a new drug application (NDA) for market authorization.

21 USC 353(g) (503(g) FD&C Act): Exemptions and consideration for certain drugs, devices, and biological products. It states in the case of combination products that the PMOA dictates lead agency and regulatory regime.
Devices: Regulated by 21 CFR parts 800–898 under CDRH, requires a premarket approval application (PMA) for market authorization.

Biological products: Regulated by 21 CFR parts 600–680 under CBER, requires a Biologics License Application (BLA) for market authorization.

The center which receives the premarket application will determine the PMOA (most important therapeutic action) of the product and assign the lead center accordingly. The OCP consults, resolves disputes, and ensures timely review.

No specific GMP guidelines exist for combination products so each set apply: 21 CFR parts 210 and 211 for finished pharmaceutical and drug products, and/or 21 CFR part 820 for devices. Parts of biological product regulations may apply (21 CFR 600–680), but there are no GMP requirements specifically referenced for HCT/Ps. For clinical investigations of combination products, typically only one investigational application is required. This is either an IND application (21 CFR 312) or Investigational Device Exemption (IDE) (21 CFR 812). The objectives of the IND review are to assure the rights of subjects and the quality of scientific evaluation of the product. This includes study approval by an Institutional Review Board and following the principles of good clinical practice.

**Table 21 Code of Federal Regulations Parts 600–680 Biological Products (21 CFR 600–680)**


Table 14.3 Regulation of RM products in Canada: biologic drugs

**Introduction**

Health Canada’s (HC’s) Health Products and Food Branch (HPFB) is responsible for the oversight of therapeutic products. It executes its regulatory responsibilities through the Therapeutic Products Directorate (TPD) for drugs and devices, and the Biologics and Genetic Therapies Directorate (BGTD) for biologics, cell, and genetic therapies. It also maintains the Therapeutics Products Classification Committee (TPCC), which can be consulted to make recommendations on the classification of products and the development of related policies. There are two main categories of products in the Canadian system: drugs and devices. A subset of the drug category is the biologic drug, which has been interpreted to include cell-based products. There are currently no specific regulations that deal with combination products or cell therapy products. HC relies on policy which utilizes the product’s principal mechanism of action (PMOA) for classification.

**Food and Drugs Act**

The Food and Drugs Act 1985 is the enabling legislation for the regulation of health products. Part I of the Act outlines restrictions for the sale of food, drugs, cosmetics, and devices. Part II deals with administration and enforcement, such as inspections and marketing authorizations. Schedule D identifies drugs categorized as biologics. While not specifically listed, cell-based products are considered by HC to be Schedule D biologic drugs. The Act is implemented via Regulations: Food and Drug Regulations; Medical Devices Regulations 1998; Safety of Cells, Tissues and Organs [CTO] for Transplantation Regulations 2007; Natural Health Products Regulations 2003; and Processing and Distribution of Semen for Assisted Contraception Regulations 1996.

The Food and Drugs Act does not specifically mention combination products. The policy adopted states that where the PMOA by which the claimed effect or purpose is achieved by pharmacological, immunological, or metabolic means (in vivo), the combination product will be subject to the Food and Drug Regulations; otherwise it will be regulated under the Medical Device Regulations. As such, cell-based products will primarily fall under Food and Drug Regulations, specifically Part C – Drugs. The sponsor would either apply to the TPD or the BGTD for classification. The Directorates will consult, and if they cannot agree, it is referred to the TPCC.

**Supplemental information:**

Modernization of Canada’s regulatory regime is currently underway, involving a comprehensive review of the regulatory framework in order to create a more flexible system with common principles that apply across product lines.

Safety of Cells, Tissues and Organs for Transplantation Regulations apply only to minimally manipulated cells and tissues. It does not apply, for example, to non-homologous use, autologous use, medical devices with cells (Part 3 Medical Devices Regulations), or cells and tissues used in a clinical trial (Part 5 Food and Drug Regulations).

Policy: Drug/Medical Device Combination Products, Effective Date: 2006/03/01
### Food and Drug Regulations Part C

Food and Drug Regulations state no person shall sell a drug that is not labeled as required by these Regulations, which includes the need to apply for and receive a Drug Identification Number (DIN). The introduction also outlines adverse reaction reporting requirements.

Part C Division 1A describes the process for applying for an establishment licence. It defines activities for which GMP compliance is to be demonstrated before the issuance of a drug establishment licence. Part C Division 2 details the GMP required for the sale of a drug. GMP guidance was written with the view to harmonize GMP standards with those from other countries and international organizations. Mutual Recognition Agreements (MRAs) establish recognition of GMP compliance certification between regulatory authorities that are designated as equivalent.

Part C Division 5 details the requirements for the clinical trial application (CTA) that requests permission to distribute the drug to investigators for use in clinical trials involving human subjects. The CTA contains information regarding the objectives of the proposed trial and data to support product quality. If benefits outweigh the risks, a No Objection Letter is issued. Trials require informed consent and good clinical practice. Research Ethics Board approval must be obtained at each institution and sponsors should register their clinical trials.

Part C Division 8 describes the requirements for new drug submissions. A new drug submission shall contain sufficient information and material to assess the safety and effectiveness of the new drug (including ingredients, locations, clinical effectiveness, labels, etc.). A Notice of Compliance (NOC) is issued after satisfactory review of a submission, finding the benefits outweigh the risks of the product. If a NOC has been issued the manufacturer must maintain records for the potential audit of any information. Upon receipt of a NOC, a DIN will be assigned.

DIN is a unique eight-digit number that permits the manufacturer to market the drug in Canada. Lets users know the product has passed review and serves as a tool to track the product.

For Biologics, Radiopharmaceuticals and Genetic Therapies: in addition to the standard drug requirements, sponsors must include more detailed chemistry and manufacturing information. In addition, the new drug submission process requires Product Specific Facility Information (manufacturing methods) and an On-site-Evaluation Inspection. If a NOC and DIN are obtained, products are monitored through a lot release schedule where for higher-risk products each lot is tested and additional surveillance is performed.

A Notice of Compliance with conditions (NOC/c) may also be issued under the NOC/c Policy. It requires the sponsor to undertake additional studies to confirm the clinical benefit of the product. It is restricted to promising new drug therapies for serious conditions with no alternative therapy or that will offer a significant improvement on risk-benefit.

---

expertise (Bravery 2010: S792). Unfortunately, regulatory bodies are often ‘chronically under-funded’ and their capacity – including expertise, personnel, and financial resources – cannot keep pace with the demands made of them (von Tigerstrom 2011: 117–20). This may present a significant barrier to progress.

Ultimately, the ability of a regulatory system to recognize and manage the potential hazards of RM products is central to its success. With new technologies come new and unknown risks, and regulators are tasked with balancing these risks with benefits to patient health (Messenger and Tomlins 2011: H11; Bravery 2010: S793–S794). When assessing risk-benefit, all the complex steps moving from bench to bedside are relevant and consequently inform ethical decision-making (Hyun 2010: 74). The establishment of sufficient trial end points, post-trial follow-up, and trial registries will be essential to determining long-term patient outcomes and for future evaluations of risk and benefit (Trommelmans et al. 2009: 464). Clinical trial registries add to the information base, and are increasingly encouraged or required by regulatory bodies (Health Canada 2013; Isasi 2009b; US National Institutes of Health 2013). Similarly, post-market surveillance is important because RM products are less predictable in the long term (Oerlemans et al. 2013: 46). The collection and utilization of this type of data to inform safety evaluations should be an industry priority.

While regulatory frameworks must be ‘alive’ to innovation, they must also be ‘conservative’ in order to ensure patient safety in a potentially high-risk area like RM (Harmon et al. 2011: 4). Regulatory reforms are needed to make existing systems more efficient and effective, but it is important to remember most therapies are found wanting during clinical trials (Werner et al. 2012: 100). This is an issue of science rather than of regulation. Uncertainty regarding data requirements comes from an incomplete understanding of the science underlying a product, and for any new technology the challenge is to determine what data is required to show safety, efficacy, and quality (von Tigerstrom 2011: 120). This is a natural part of the industry applying scientific developments in emerging technologies, and it is expected that many of these issues will be resolved through technological improvements and more research into the science (BIS 2011: 33).

When discussing what the emerging field of RM needs from its regulatory system, many would agree that a clear regulatory framework, even if strict, is paramount (Plagnol et al. 2009: 554). However, it is also important to keep in mind that technocratic reactions to new science are cumulative, and increased regulatory demands do not necessarily result in better decisions (Harmon et al. 2011: 4). This would imply that being too aggressive in the application of complex legal and regulatory measures at the early stages is ill advised. Finding the appropriate balance is the task at hand.

14.5 Conclusion

The advancement of RM science offers the potential for cutting-edge solutions to healthcare challenges, but will require concerted efforts in policy and regulations to ensure these solutions are safe and socially beneficial. Ethical, legal, and social justice issues arise from various aspects of the technology, such as from the use of human cells (which are variable and risky), from the clinical translation of novel and complex products, and from the commercialization of publicly funded research. These areas have been explored and guidelines have been developed to aid the innovation process. However, gaps exist and questions regarding the validity of the informed consent of participants and of public awareness at all stages of research and development pervade assessments of the industry. Clear and effective regulatory regimes provide a mechanism to mitigate some of the potential negative consequences of RM innovation. Regulations ensure that
products entering the market are of high quality and are safe and effective. Unfortunately, the long, complicated and expensive regulatory pathways currently in place for existing therapies are often unsuitable for the complex cell-based products in development, and unbearable to the SMEs developing them.

Crafting regulatory systems appropriate for RM products is now the challenge. Governments recognize this task, and are beginning to create new regulatory bodies and regulatory categories able to address the unique nature of RM innovations. These efforts have been mindful of the importance of standards in manufacturing and clinical testing. As the science and regulations co-evolve, industry and regulators will need to be cognizant that international harmonization is equally important in this global, interdisciplinary, and fast-paced field.

References


BIONET (2010b) 'Recommendations on Best Practice in the Ethical Governance of Sino-European Biological and Biomedical Research Collaborations (BIONET Expert Group Report March 2010),' viewed 18 April 2013 at: http://www.lse.ac.uk/researchAndExpertise/units/BIONET/.


Bubela, T., Li, M. D., Hafez, M., Bieber, M., and Atkins, H. (2012) 'Is belief larger than fact: expectations, optimism and reality for translational stem cell research,' BMC Medicine, 10: 133.


Carla Beak and Rosario Isasi


Legislation

Food and Drug Regulations, CRC, c. 870 (Canada).
Food and Drugs Act, RSC 1985, c. F-27 (Canada).
Medical Devices Regulations, SOR/98–282 (Canada).
Carla Beak and Rosario Isasi

Natural Health Products Regulations, SOR/2003-196 (Canada).
Processing and Distribution of Semen for Assisted Conception Regulations, SOR/96-254 (Canada).
Public Health Service Act (1944) 58 Stat. 682 (US).

Cases