Review

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Regenerative Medicine

Current practices and reform proposals for the regulation of advanced medicinal products in Canada

We describe the Canadian regulatory framework for evaluating advanced medicinal products based on current policies, guidance documents and regulations and analyze proposed reforms. Our analysis is based on a documentary review supplemented by discussions with Health Canada officials. We present an overview of the Canadian regulatory framework for cell and gene therapy, medical devices and manufacturing facilities. We use the approval of Prochymal™ to highlight Canada's conditional marketing approval system. Finally, we discuss proposed changes to the regulatory framework in response to identified gaps, stakeholder consultations and international harmonization initiatives. Based on our analyses, we suggest that Canadian regulators have taken a reasonable approach in applying their regulatory framework without compromising on product safety.

Keywords: accelerated market approval • advanced medicinal products • cell therapy • clinical trial • gene therapy • Health Canada • market approval • medical device • orphan drug framework • regulation • regulatory reform

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Regenerative medicine research and clinical translation has had a significant presence in Canada, extending as far back as 1961 when James Till and Ernest McCulloch pioneered the field of stem cell research with their publication of a method to quantify putative progenitor and stem cells [1]. Regenerative medicine research has been supported by multiple federal initiatives including the Stem Cell Network, funded from 2001 to 2016 by the Networks of Centers of Excellence (NCE) program, which has brought together researchers, bioengineers, clinicians and social scientists to move Canadian stem cell research to clinical application (Stem Cell Network, 2014). Now in its final 2 years of funding, the Network has left a strong legacy of research in Canada, and while the network did not directly fund clinical trials, clinical trials using stem cells and other cell types are ongoing across the country. As of April 2015, there are approximately 46 cell therapy clinical trials ongoing, enrolling or planned in Canada (Supplementary Table 1; see online at www.futuremedicine.com/doi/full/10.2217/RME.15.28); a further nine are completed and five were listed as terminated or unknown. Most trials (n = 33) are in cancers and most are early stage (Phases I, I/II or II); 11 are listed as Phase II/III or III but only three of these are underway.

Further support is provided by the Canadian Stem Cell Foundation, an independent, nonprofit charitable organization was founded in 2008 to fund and champion stem cell research in Canada. Further support for the clinical and commercial development of regenerative medicine comes from the Centre for Commercialization of Regenerative Medicine (CCRM) in Toronto, founded as a not-for-profit organization and supported by the Centers of Excellence for Commercialization and Research (CECR) program [2]. The most recent round of NCE funding has supported BioCanRx, which is focused on the clinical translation of novel cancer biotherapeutics, including immunotherapies and cancer vaccines and by the creation of CellCAN [3], a

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pan-Canadian network of cell manufacturing facilities aimed at accelerating cell-based clinical trials in Canada.

As these funding initiatives and strong research programs and networks have developed in Canada, novel therapeutic products are beginning to emerge clinically. It is therefore timely to consider the regulatory pathways for regenerative medicine products and other novel biotherapeutics (e.g., oncolytic viruses or antibodies in cancer therapies) in Canada. These are regulated as advanced medicinal products (AMPs) under the Food and Drug Act [4], primarily by Health Canada's Biologics and Genetic Therapies Directorate, which is responsible for the regulation of biological drugs for human use in Canada based on sound evidence of the product's quality, safety and efficacy. There are a number of regulations (Figure 1) that may apply to advanced medicinal products including the Food and Drug Regulations [5], Safety of Human Cells, Tissues and Organs (CTO) for Transplantation Regulations [6] and the Medical Devices Regulations (MDR) [7]. For embryonic stem cells, certain provisions of the Assisted Human Reproduction (AHR) Act of Canada apply [8], including prohibitions on creation of embryos for research purposes, and the need to obtain permission to conduct research on embryos that are no longer required for fertility treatments upon full, informed consent of donors.

Here, we provide a detailed explanation of each regulatory pathway in Canada for AMPs, provide specific examples of AMPs that have met the definitions and have been evaluated through one or more of these pathways and discuss proposed reforms for the regulatory framework for AMPs. Our analysis is based on a documentary review supplemented by discussions with Health Canada officials about the application of current policies, guidance documents, regulations and statutes that govern cell and gene-based therapies. Officials additionally shed light on gaps in the framework that might be addressed by future policies or guidelines.

AMPs may follow a number of different regulatory pathways. An AMP is regulated under the CTO regulations [6] if it is used for allogeneic purposes, is minimally manipulated and meets other criteria. This regulation is akin to the 21 Code of Federal Regulations 1271 in the USA [9], and European Union (EU) Directives 2001/83/EC and 2009/120/EC [10,11]. For example, allogeneic bone marrow transplantation, where bone marrow cells from a donor are used to replace bone marrow cells in the host, falls under the CTO regulations. If the AMP has metabolic and systemic effects, it falls under the Food and Drug Regulations [5], for example, a stem cell therapy product such as Prochymal®, which has been approved in Canada for the treatment of pediatric, acute, steroid-refractory graft-versus-host disease (GvHD). An AMP that does not meet the definitions of a CTO or the Drug Regulations, may be regulated under the Medical Device Regulations. Alternatively, it may be a combination product, such as Viacyte's VC-01, which was recently approved for clinical investigations in the USA and Canada. The flow chart in Figure 2 explains the classification process and the application of different regulations in Canada.

Regulations for cell therapies: cells, tissues & organs for transplantation

Minimally manipulated allogeneic cells, tissues and organs that meet certain criteria fall under the CTO regulations [6]; no specific evidence of efficacy need be provided to Health Canada under these regulations. Minimal manipulation is defined as processing that does not alter the biological characteristics

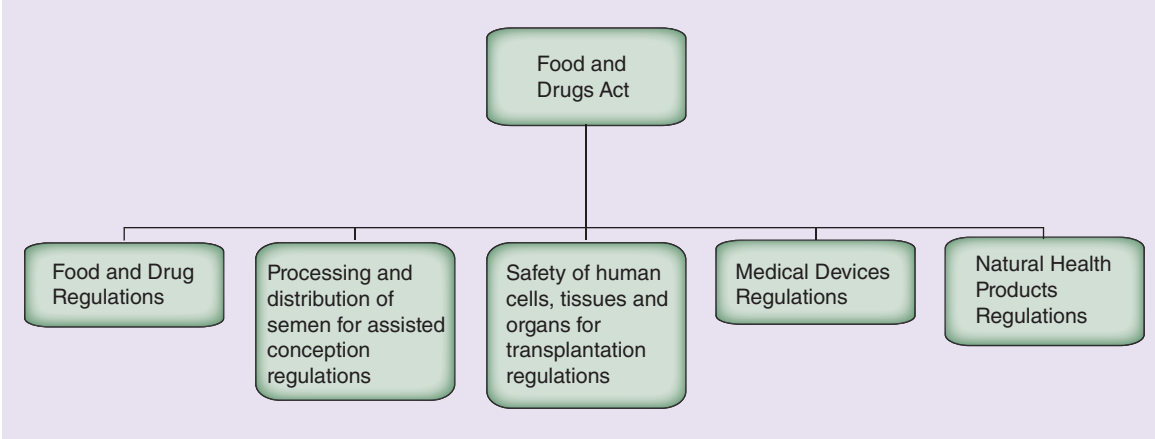

Figure 1. Under the Food and Drug Act, there are several regulations that may be applied to cell and gene therapy products.

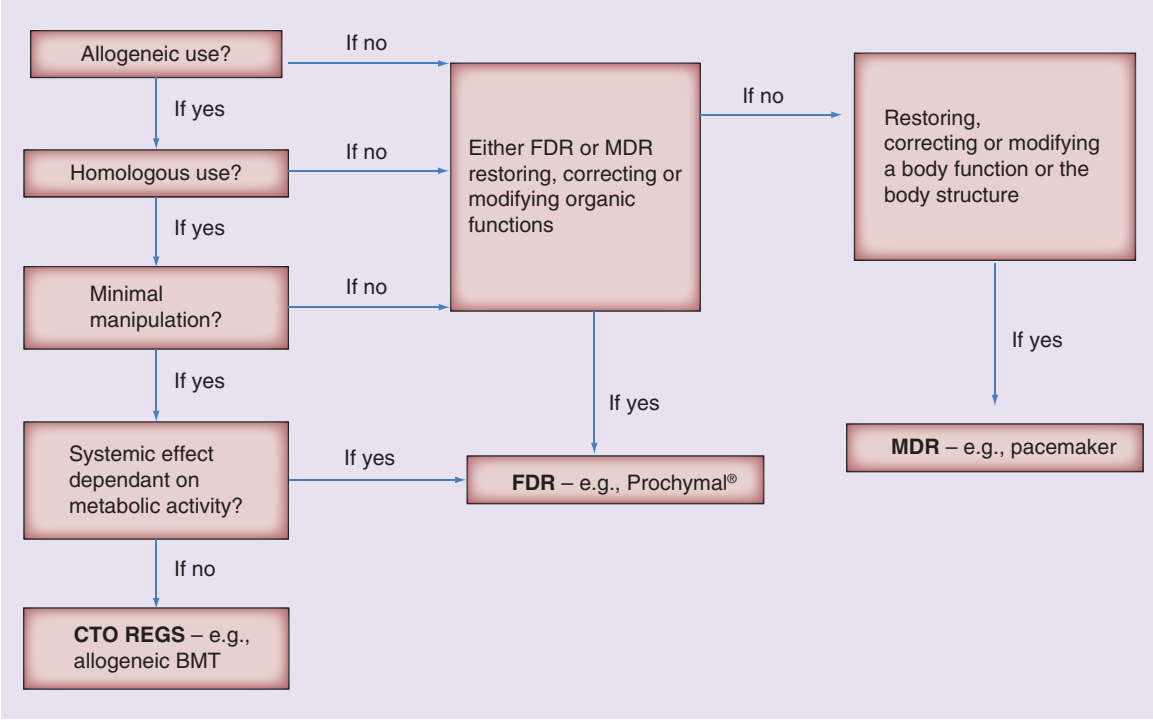

Figure 2. Simplified decision tree to classify advanced medicinal products as cell, tissues, organs for transplantation purposes, as drugs under Food and Drug Regulations or as medical devices under Medical Device Regulation.

AMP: Advanced medicinal products; CTO: Cell, tissue, organ; FDR: Food and Drug Regulation; MDR: Medical Device Regulation.

of the cells, tissues or organs that are relevant to the claimed utility of those cells, tissues or organs. In addition to minimal manipulation, for CTO regulations to apply, the cells, tissue or organs must be intended for allogeneic use, defined as transplantation from one individual to another. CTO guidelines further clarify that the regulations are applicable for homologous use, nonsystemic/nonmetabolic effects, and that the product should not be combined with non-cell or non-tissue products [12]. Typically, many of the products may had their safety and effectiveness previously demonstrated through historical use or clinical studies.

The CTO regulations came into effect in December 2007, and updates to the CTO Guidance Document were released in June 2013 [12]. Establishments that process CTO products must be registered with Health Canada and are subject to inspections to monitor compliance with the regulatory requirements discussed below. The CTO Regulations are standards-based (Z900 1–2 package), promulgated by the Canadian Standards Association [13]. A committee of transplantation experts and other stakeholders develop these standards by consensus and evaluate and update them on an on-going basis. Importantly, there are no requirements for formal premarket review or approval of CTO products; CTO products however need to be compliant with national standards under the CTO regulations, and must meet documentation requirements for evidence of such compliance to ensure traceability.

The current application of the CTO regulations, however, leaves an important gap that is addressed in other jurisdictions. Namely, minimally manipulated, but autologous cell products that may otherwise satisfy all the CTO criteria would not be regulated under the CTO Regulations, and their investigational use would instead fall under Part C, Division 5 of the more onerous Food and Drug Regulations [4]. These stipulate the requirements that drugs must meet, including conducting authorized clinical trials. Problems may arise because autologous cell products often do not require clinical trials, falling instead within the practice of medicine. Other jurisdictions have provided regulations to deal with this gap; in the USA there are written exceptions to compliance with the Code of Federal Regulations, Title 21, Part 1271 if human cells, tissues and cellular and tissue-based products are removed from an individual and implanted into the same individual during a surgical procedure [9]. Given that this procedure applies to a relatively small subset of products, with arguably low risk, the regulatory gap has been allowed to persist in Canada, although there have been previous suggestions for alternate approaches [14]. Health Canada is aware of this gap; it encourages

sponsors to discuss and clarify the regulations that may apply to their specific products. However, clear guidelines and regulations will improve the regulation of these products and limit any inappropriate use.

Regulations for cell therapies: Food & Drug Regulations

Cell products that are more than minimally manipulated or that do not otherwise meet CTO criteria are subject to either Food and Drug Regulations [5], or Medical Device Regulations [7], or as a combination product depending on their classification (Figure 1). Given that most cell therapy products are likely to have some systemic and/or metabolic effect, it is unlikely that most will meet the CTO criteria. Such cell products are therefore subject to clinical trials, according to Part C, Division 5 of the Food and Drugs Regulations [5].

Some cells, however, are regulated under CTO despite not meeting CTO criteria because they are specifically exempted (i.e., islet cells and lymphohematopoietic cells from cord blood, bone marrow or peripheral blood). For example, consider lymphohematopoietic cells that are isolated from a bone marrow aspiration. If these are used for allogeneic transplant or banking purposes (Figure 3), they would fall under the CTO regulations. If, however, they are used for autologous transplant or banking purposes (Figure 3), they should fall not under CTO regulations, but under the more onerous drug regulations. Fortunately, these cells were grandfathered and fall under the CTO regulations as exemptions. The isolation of $CD34^+$ lymphohematopoietic cells is also considered minimal manipulation as the cells are not culture expanded; there is also significant clinical evidence associated with this type of therapy (Figure 3). However, if the same $CD34^+$ lymphohematopoietic cells are minimally manipulated, and used for nonhematopoietic purposes, such as treating patients' postmyocardial infarction (MI), the situation is different. Such use is considered nonhomologous and is therefore regulated under the Food and Drug Regulations (Figure 3). Similarly if bone marrow aspirate is used for isolation and expansion of MSCs, it would be considered more than minimal manipulation, and thus be regulated under the Food and Drug Regulations (Figure 3). For example, Health Canada reviewed and regulated Prochymal®, an allogeneic, culture-expanded bone marrow derived MSC product from Osiris, under the Food and Drug Regulations (see section below on Cell and Gene Therapeutics that have Received Approval by Health Canada).

Investigational use of cells that are regulated under the Food and Drug Regulations requires specific Health Canada authorization. To obtain such authorization, a clinical trial application (CTA) must be submitted before initiating each of Phases I–III clinical trials. Once submitted, the CTA is reviewed within 30 days default by a clinical and quality review team (laboratory, if applicable). Health Canada will issue a 'no-objection' letter (NOL) if there are no outstanding issues allowing the trial to commence with appropriate local research ethics board (REB) approvals. If there are deficiencies, Health Canada may issue several clarification requests (Clarifax); sponsors need to respond to Clarifaxes within a 2-day period. If the responses are not satisfactory, Health Canada may issue a Non-satisfactory Notice (NSN). Sponsors may respond, but are required to submit a new CTA, initiating another 30-day review process [15].

Health Canada has recently issued a draft guidance on preparation of CTAs for use of cell therapy products in humans [16]. There are also guidance documents on submission of a CTA, and on presubmission consultation meetings with regulators [17].

Given that the starting donor material is arguably the most important determinant of cell therapy product quality, safety and efficacy, special care needs to be paid to the screening and testing of the starting material. Many of the basic donor screening and testing requirements under the CTO regulations can also be applied to screening and testing for investigational use of cells under the Food and Drug Regulations. The

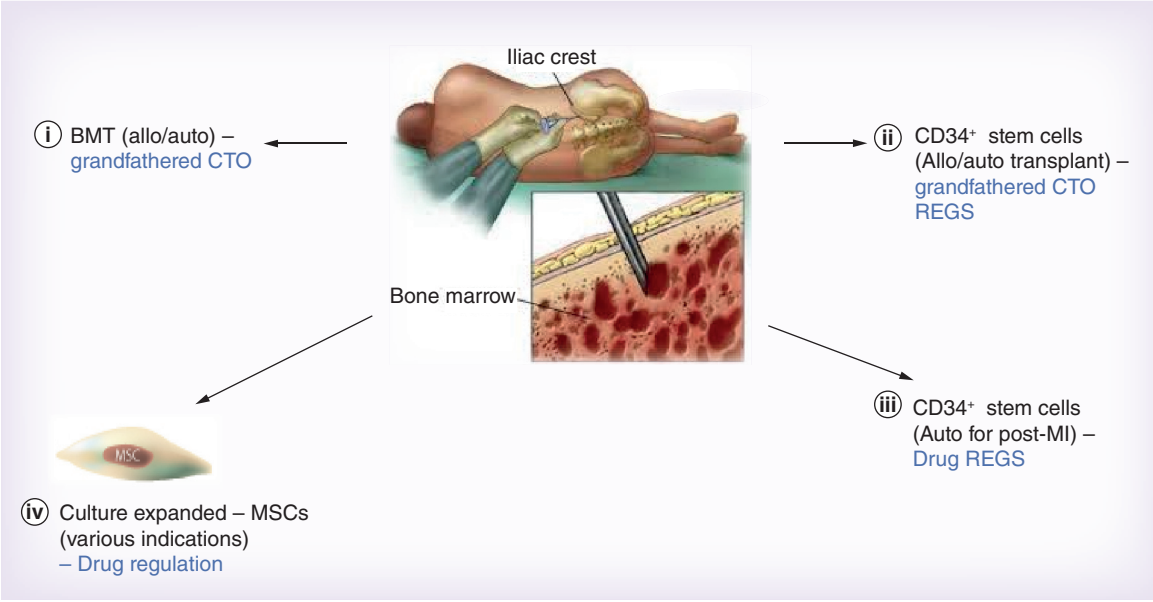

Figure 3. Bone marrow aspirate can be used as bone marrow transplantation which is homologous and minimally manipulated, although it has systemic effects; it is grandfathered under the cell, tissue, organ regulations. $CD34^+$ cells isolated from bone marrow aspirates can be used for transplantation and would also be grandfathered under CTO REGS. $CD34^+$ cells used for other indication such as treatment of postmyocardial infarction patients would fall under Food and Drug Regulations. Bone marrow aspirate used to culture expand mesenchymal stromal cells would fall under FDR.
BMT: Bone marrow transplantation; CTO: Cell, tissue, organ; MSC: Mesenchymal stromal cell; Post-MI: Post- myocardial infaction.

new draft guidance for cell therapy products [16] provides some flexibility by allowing for justifiable deviations from these screening procedures due to logistical or safety reasons. There also guidance documents on minimizing risk for transmissible spongiform encephalopathies (TSE) by use of animal-sourced materials [18].

Health Canada, through its Clinical Trials Database [19], provides to the public a listing of specific information relating to approved Phase I, II and III clinical trials. The database is managed by Health Canada and provides information about Canadian clinical trials involving pharmaceutical and biological drugs for human use. The database may assist Canadians in finding clinical trials that might be relevant to their medical condition. However, the database only lists trials from 1 April 2013 for drugs, but not natural health products or medical devices. It is not a registry and does not contain comprehensive information about each trial. Users are referred to other registries including clinical.trials.gov, and the international standard randomized controlled trial number (ISRCTN), as well to cancerview.ca (a Canadian-based registry of cancer trials).

Once sufficient clinical safety and efficacy data is generated, the sponsors of clinical trials may submit an application, called the new drug submission (NDS) to Health Canada for market approval and authorization of their drug. A separate establishment license (EL) application (for Canadian manufacturing facilities and importers of foreign manufactured health products) may be made to the Health Products and Food Branch Inspectorate (hereinafter, Inspectorate), and if the facility is found to be compliant with Good Manufacturing Practices (Part C, Division 2 of the Food and Drug Regulations), an EL may be issued. We discuss these procedures in more detail below in the sections on Market Authorization Process for Drugs and the Regulation of Manufacturing Facilities, respectively.

Regulations for gene therapy products: Food & Drug Regulations

There have been a number of clinical trials using gene therapy medicinal products to treat monogenic disorders, cancers and infectious diseases [20,21]. The field is undergoing a revival with newer, safer vector designs. Initial enthusiasm was dampened by allegations of misconduct, the high-profile death of a clinical trial participant at the University of Pennsylvania [22], and incidences of insertional mutagenesis in a trial for treatment of X-linked severe combined immunodeficiency (X-SCID) [23]. However, recent advances in monogenic retinal disorders appear promising [24,25].

Additionally, emerging immunotherapies using genetically modified, patient-specific T cells to target specific antigens or proteins expressed by cancer cells are also generating a new wave of excitement. CAR

T-cell therapy uses the patient's own T cells with a synthetic receptor that recognizes proteins on certain cells, such as malignant B cells. Fifteen clinical investigations with CAR-T's have been published in the last 5 years, mostly focused on advanced B-cell malignancies, including chronic lymphocytic leukemia, acute lymphoblastic leukemia, non-Hodgkin lymphoma (NHL) such as diffuse large B-cell lymphoma with very promising response rates [26–31], in some cases as high as an 89% response rate [32].

Health Canada does not have specific guidelines or regulations pertaining to gene therapy, however gene therapy products are regarded as biological drugs, and thus typically fall under the Food and Drug Regulations [5]. Health Canada refers sponsors to International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) guidelines, (Health Canada is a member of ICH's Steering Committee) including those for safety testing of vectors [33] and three consideration documents on general principles to address viral/vector shedding [34], inadvertent germline integration [35] and oncolytic viruses [36]. The US FDA also puts out excellent guidance on the production, characterization and release testing of vectors for gene therapy [37], and a recent draft guidance on conducting shedding studies during preclinical and clinical development for viral and bacterial based gene therapy products and for viruses and bacteria (38).

In addition to the considerations for cell therapies, additional safety and stability information needs to be provided to regulatory agencies on the vectors that are used either alone or to transduce cells. This information should allow the sponsors to address concerns on the possible generation of replication competent viruses, spread of genetic material beyond target tissue and patients, specificity of targeting *in vivo* and level of gene expression and the use of appropriate animal models to demonstrate safety and efficacy.

Insertional mutagenesis with integrating viral vectors remains a concern, and the European Medicines Agency (EMA) has put out a reflection paper to discuss what factors contribute to this rare event, and how vector designs may reduce the risk, and what integration studies and nonclinical animal studies may be performed to assess the risk [39]. New techniques using endonucleases like artificial zinc finger, TALEN nucleases or CRISPR [40] may mitigate the risk from random or semirandom insertions [41].

Glybera® is the only gene therapy product, worldwide that has received market authorization, albeit under exceptional circumstances. UniQuire, the sponsor applied for market authorization in the EU and was rejected by the Committee for Human Medicinal Products (CHMP) three-times. The CHMP carries out scientific reviews for human drugs in the EMA and makes recommendations for market approval by the EC. The CHMP finally approved Glybera after a fourth review. Glybera received market authorization from the EC in 2012 for use under exceptional circumstances. It is authorized for use for "adults with lipoprotein lipase deficiency who have severe or multiple attacks of pancreatitis (inflammation of the pancreas) despite maintaining a low-fat diet" [42]. The approval is contingent on substantial postmarketing requirements; it allows commercial sale of the product with ongoing evaluation of product safety and efficacy.

Importantly, in its review of Glybera, CHMP was not unduly concerned about gene toxicity or manufacturing issues [43]. Instead, the focus was on proving efficacy, which was difficult to prove because of the ultraorphan disease status of LPL (one in 1 million), making it difficult to recruit sufficient patients for the efficacy studies. Efficacy results were based on 27 patients in three clinical trials in The Netherlands, and Quebec, Canada, where prevalence is higher due to a founder effect [43]. Glybera has received orphan drug designation in the USA, and the company that developed it, uniQure, plans to file a Biologics License Application (BLA) with the US FDA after completing a planned Phase IV trial, which is expected to commence in 2015. uniQuire also plans to file market authorization in Canada.

Medical devices for diagnostics/delivery of cell or gene therapies

Medical devices, defined in Food and Drug Act [4] as "restoring, correcting or modifying a body function or the body structure of human beings or animals," are regulated under the Medical Device Regulations [7] and reviewed by the Medical Devices Bureau of the Therapeutics Products Directorate of Health Canada. Medical devices can range from laboratory and diagnostic kits to pacemakers and other therapeutic devices. Medical devices are classified into four classes, class I–IV, depending on risk levels. Class I device examples include low-risk devices, such as a thermometer. Class II devices include low-to-moderate risk devices such as guide catheters. Class III devices are moderate-to-high risk and include implants such as orthopedic implants, while class IV are highest risk devices such as pacemakers.

Scaffolds or combination of biologics with cells need to be appropriately classified as drugs, devices or combination products. A centralized committee called the Therapeutics Product Classification Committee uses the statutory definitions to determine whether a product is classified as a drug and falls under the Food and Drug Regulations [5], or as a Medical Device (under Medical

Devices Regulations). The Committee is consulted in cases where issues of classification are not apparent or easily decided between the sponsor and Health Canada or within Health Canada internally. Essentially products that have a pharmacological, immunological or metabolic *in vivo* effect are typically classified as drugs. Examples of combination products that are classified as drugs include prefilled syringes, whereas drug-eluting stents are considered as devices. According to Health Canada policy, such combinations must comply with either drug or device regulations, but not both, although there are exceptions to this policy for example a first aid kit must comply with both regulations.

An example of a combination AMP is VC-01 from Viacyte, Inc. VC-01 contains embryonic stem cell derived endodermal cells, which mature and differentiate to synthesize and secrete insulin and other factors. The cells are surrounded by a pouch comprised of a semi-permeable membrane that keeps the endodermal cells inside, the host immune cells outside and only allows for exchange of nutrients and secreted factors [44]. The endodermal cells inside the pouch would fall under Drug Regulations, while the pouch as a physical barrier would fall under Medical Device Regulations. Viacyte, Inc. received FDA approval for a Phase I/II safety trial in 40 patients in August 2014, and received an NOL from Health Canada in January 2015.

Class II–IV medical devices require a license before sale or advertising, as specified in the Medical Device Regulations. Medical devices that are used within a hospital and for which there is no sale or advertisement, are thus exempt under the current interpretation of the regulations. This means any device that is used in an in-hospital or in-clinic services, which are not advertised or sold in any format may be exempt from the Medical Device Regulations. Health Canada officials see this as a gap in the current regulation and think this gap may be exploited to introduce cell-based medical devices which offer on-site processing, including certain cell isolation and purification devices or 'Good Laboratory Practice (GLP)-in-a-box' without any regulation or oversight. Since these devices essentially perform a service (processing cells) and if these services are not sold or advertised, the devices may be exempt from current regulations. Similarly, surgical procedures are considered practice of medicine, and do not require Health Canada licensing. Any on-site isolation, processing and turnaround of cells during a surgical procedure that is not advertised could thus be technically exempt.

Approval for medical devices is obtained upon full risk/benefit review by the Medical Devices Bureau of the Therapeutic Directorate. A full medical device license application needs to be submitted; typically class II devices require a 15-day review period, and class III and IV devices require a 75–90-day review. Class I devices are exempt from a medical device license, but their manufacturers, importers and distributors are required to have an Medical Device Establishment License (MDEL) with Health Canada. An MDEL allows regulators to monitor the premises, and we discuss this type of license in more detail in the section on Regulation of Manufacturing Facilities, below. Class II–IV devices are required to provide increasing evidence of safety and efficacy with class of medical device.

Manufacturers of class II–IV medical devices need to show compliance of their facility against ISO 13485 standards. Compliance to ISO 13485 is demonstrated by issuance of a quality system certificate by third party auditing organizations recognized and registered under the Canadian Medical Devices Conformity Assessment System. There are currently 19 Health Canada recognized registrars [45], which can perform this audit function. Typically, manufacturers of class II–IV devices do not need an MDEL for manufacturing but require one for other licensable activities such as importing or sale of a licensed medical device.

Laboratories providing diagnostic testing for cell-based therapies

Laboratories that perform diagnostic testing and/or testing on cell therapy products prior to their utilization in clinical investigations or as part of final lot release of commercial products are also regulated by various guidelines and agencies. Typically, diagnostic kits fall under Health Canada requirements under Medical Device Regulations prior to market authorization; testing services offered by a laboratory, on the other hand, fall outside the Medical Device Regulations (there is no sale here), and are under provincial purview. Jurisdiction over health and services is split between the Federal Government (e.g., Health Canada) and the Provincial Governments. The Provinces have jurisdiction over the delivery of healthcare and laboratory services, and therefore, the regulation of diagnostic testing services is not uniform across the country.

- For six provinces, there are specific laws to obtain a government-issued laboratory license. For example, in Ontario a Laboratory license from the Ontario Ministry of Health and Long-Term Care under the Laboratory and Specimen Collection Centre Licensing Act and Ontario Regulation 682 allows the lab to perform specific tests. These include, for example, bacteriology, biochemistry, virology, serology, HIV antibody, cytogenetics, cytology, hematology, histology, immunoassays, immunohematology, immunology, molecular genetics and mycology. The facility is then subject to inspec-

tion by the Laboratory Licensing and Inspection Service of the Ministry. Other provinces that have licensing requirements are Quebec, Saskatchewan, Manitoba, Newfoundland and British Columbia. The remaining provinces do not have government licensing requirements;

- In addition to licenses, most laboratories are accredited by a recognized governing body. In Ontario, the Ontario Laboratory Accreditation (OLA) Program is the mandatory program for all licensed medical laboratories in Ontario. The OLA requirements are based on international standards including ISO 1518:2007, ISO 15190:2003 and ISO 22870:2006. In Alberta, the College of Physicians and Surgeons of Alberta (CPSA) runs a medical facility accreditation program; in Manitoba the Manitoba Quality Assurance Accreditation (MANQAP) Program is run by the College of Physicians and Surgeons of Manitoba; in Quebec the Bureau de normalization du Quebec under the authority of the Standards Council of Canada (SCC) accredits laboratories, and British Columbia has a Diagnostic Accreditation Program. There are also international quality systems and accreditation programs including ISO 13485 Quality Management Systems, which is an international standard that allows an organization to demonstrate its ability to provide medical devices or related services on a consistent basis; College of American Pathologists Laboratory Accreditation Program, which is an internationally recognized program; and FACT (Foundation for Accreditation of Cellular Therapy) for transplantation programs and cord blood banks;

- The laboratory may also need to meet federal requirements, for example, an EL from Health Canada (for specific regulated activities such as testing drugs. We outline these requirements in the section on Manufacture of Cell and Gene Therapies and Regulation of Manufacturing Facilities.

The laboratories are thus frequently inspected on a routine basis by one or more organizations/agencies and assessed against criteria of quality management systems, methods, equipment, personnel, training and general procedures. Each accreditation or license is meant to authorize the laboratory for specific activities; a laboratory may require multiple authorizations from different bodies to perform multiple services including testing drugs, diagnostics, donor screening activities on raw materials, quality control tests on drug products. For example, an accredited hospital microbiology lab may undertake multiple activities including serology and adventitious viral testing for pharmacy groups and the hospital. It therefore needs an EL. The same laboratory may undertake donor screening for the bone marrow transplant programs at the hospital, in which case it requires CTO registration and FACT accreditation. The laboratory may also undertake donor screening for maternal blood, and cord blood banking for private cord blood companies, which require CTO registration, EL and FACT accreditation. Donor and recipient screening for organ transplants requires CTO registration.

Regulation of manufacturing facilities

If a cell therapy product is regulated under CTO regulations, the facility (source establishment) that is processing, importing and distributing the cell, tissue or organ must be registered (mandatory) with Health Canada. Typically, source establishments are hospitals or blood banks, including those that process lymphohematopoietic cells derived from cord blood, peripheral blood and bone marrow. Public cord blood banks must be registered with Health Canada. Private cord blood banks may be exempt if they are banking cord blood for only autologous use, which is exempt from CTO regulations; however private cord blood banks may choose to register to make the cords available to siblings or other third parties. If the cord blood is used for nonhomologous use, is more than minimally manipulated or has a systemic effect and depends on its metabolic activity, then Health Canada authorization via a clinical trial application is needed, as specified in Division 5 of the Regulation [46] and in the new draft guidelines [17].

The regulation of cord blood raises questions about how facilities that store and process other tissues, such as lipoaspirates should be regulated. If facilities are fabricating or distributing cells for miscellaneous therapeutic use, the cells likely fall under the drug classification and would require an NOC and DIN, and the facility may require an EL. However, lipoaspirates that are minimally manipulated for homologous use are a regulatory challenge when they are done at the bedside because this activity clearly is not considered 'drug' manufacturing, and it may be considered by some to be medical practice. It is not immediately clear what regulations should govern such activities, especially if they are for autologous use. Equally, it is unclear how establishments that provide such services or procedures should be regulated. If such arguably low-risk procedures are carried out at multiple hospitals and other clinical settings, it would seem overly onerous to have each one inspected for carrying out essentially the same service or procedure. Indeed, recommendations from the late 1990s suggested that such autologous proce-

dures, which have demonstrated safety and efficacy, be regulated by practice standards developed by consensus by interested stakeholders and held to those standards of practice by valid, third-party auditing authorities [14], approved by Health Canada, and in coordination with the Inspectorate. Health Canada may be open to revisiting such out-of-the-box thinking in developing new policies as the field of autologous, minimally manipulated, homologous use therapy matures. In the meanwhile, Health Canada encourages facilities to have early discussions with it to understand the scope of proposed activities, which will inform the application of components of the regulatory framework.

The procedure for registering a facility under CTO regulations comprises more of an administrative review than an evidence-based scientific review. However, the onus lies on the facility to make available the scientific rationale and evidence for the proposed activities. The Inspectorate does inspect the facility within 24 months of registration and notes compliance and critical, major and minor observations. Depending on the degree of compliance and activity (and commensurate risk associated), the frequency of subsequent inspections are determined, as detailed in a policy document (POL-0057) [47].

If a cell therapy product falls under the Food and Drug Regulations, while it remains investigational, the manufacturing, handling and storage of the cell product (if defined as a drug) falls under Division 5 of the Food and Drugs Regulations [46], and requires compliance with applicable GMP, Division 2 of the Food and Drug Regulations [4] and GMP guidelines (Figure 4) [48]. However, interpretation of how these GMP guidelines are applied, especially during early phases of clinical trials is flexible without compromising product safety. This is because many clauses in Division 2 of the Food and Drug Regulations apply to authorized drugs, and not to investigative therapies. Thus the sponsors typically demonstrate GMP compliance as part of their CTA, and regulators review compliance with GMP guidelines as part of the Quality Review of the CTA process.

Regulatory requirements become more stringent and formalized through clinical development (i.e., later stage clinical trials) and once the product has completed the required clinical trials and is seeking licensure as a marketed drug, for example, under the NDS submission process (Figure 3). Under Part C, Division 1A of the Food and Drug Regulations, an EL is needed for anyone seeking to fabricate, package, label, distribute, test, import or wholesale drugs.

To obtain an EL, an application defining the type of licensable activity (i.e., fabricate, package, label, distribute, test, import, distribute or wholesale) needs to be submitted to Health Canada and usually triggers an inspection by the Inspectorate Program (Health Products and Food Branch Inspectorate of Health Canada) to verify compliance with GMP practices as outlined in Part C, Divisions 2 to 4 of the regulations [46,48]. If the manufacturing site is outside of Canada, it may be subjected to inspections or alternatively produce appropriate evidence of GMP compliance. Inspection may be performed by local regulatory authorities, and for foreign sites that are located in countries with a mutual recognition agreement (MRA) with Health Canada such inspection is accepted. The different mechanisms of showing compliance, dependent to some degree on the levels of risk associated with the product and the manufacturing process, are detailed in a guidance document (GUI-0080) [49].

Once an EL is issued, there is no expiry date for the EL, but annual reporting is required. If deficiencies are observed or reported, there is a compliance enforcement policy which outlines a detailed process for ensuring compliance [50]. Depending on the risk to public health and safety, the compliance history of the regulated party, the degree of cooperation offered, the likelihood of the problem recurring, the Inspectorate may undertake different types of enforcement actions. These may include providing a timeline for the noncompliance to be addressed or even immediate suspension of the EL. Sometimes for health risk reasons, suspensions need to be immediate; at other times, a written notification is issued to the regulated party that sets out the reason for the proposed suspension, any corrective action to be taken, and the time within which it must be undertaken.

The EL provides authority for the regulated party to perform a licensable activity; therefore, the suspen-

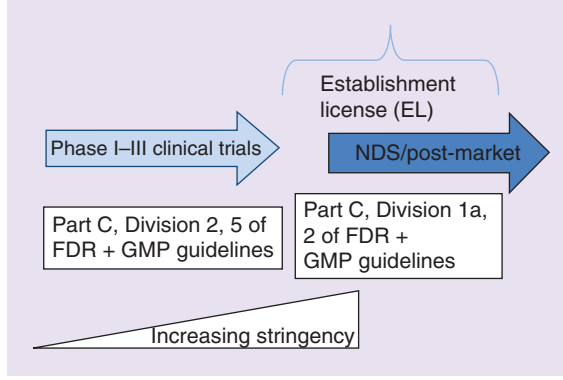

Figure 4. Good Manufacturing Practice regulations increase in stringency and formal requirement during clinical investigation and need to be in place before product licensure.
EL: Establishment license; FDR: Food and Drug Regulations; GMP: Good Manufacturing Practice; NDS: New drug submission.

sion of the EL simply means it is no longer authorized to perform those activities. Until recently, the regulated party in response to noncompliance activity and depending on the level of risk associated with the noncompliance could voluntarily choose to detain products, dispose products, stop sales or recall products. These actions can now be enforced by Health Canada following the enactment of Bill C-17 or The Protecting Canadians from Unsafe Drugs Act or Vanessa's Act [51], which provides Health Canada with the authority to intervene when such noncompliance is identified. The Food and Drugs Act and other legislation provide for additional enforcement measures, including customs activities, injunctions, prosecution, forfeiture, public warnings or advisory letters to trade organizations or regulated parties, search and seizure, search and detention and so on.

Facilities that manufacture products that fall under a medical device category may also have EL requirements, typically if they are manufacturing, importing and distributing class I devices and/or importing/distributing class II–IV medical devices in Canada, as detailed in a guidance document (GUI-0016) [52]. However, there are a number of exceptions to this requirement, for example, retailers and healthcare facilities may be exempt from EL requirements. As discussed under Medical Devices, facilities that manufacture class II, III or IV medical devices need to demonstrate compliance with ISO 13485 standards by recognized third-party auditors. There are, however, annual reporting requirements and cyclical inspections by the Inspectorate (POL-0035) [53]. Suspension of a medical device EL can occur for nonconformance reasons, similar to a drug EL nonconformance as outlined in a guidance document (GUI-0073) [54].

Market authorization process for drugs

Market authorization for a product in Canada requires the filing of a New Drug Submission (NDS) with Health Canada, as required in Division 8, Part C of the Food and Drug Regulations [5]. A guideline for drug submissions is applicable to all biologics, including cell therapies [55]. The NDS is a formatted document, and follows the ICH Common Technical Document format, it includes five sections: master volume (contains product monograph information, package inserts and label information), chemistry and manufacturing, comprehensive summary, sectional reports and raw data (for both preclinical and clinical studies).

To enable a complete review, the NDS needs to contain sufficient and substantive information on each relevant investigational clinical and preclinical study including methodology, results, conclusions and evaluation, as well as raw data, data reduction and analyses. Additionally, the product manufacturers must supply Product Specific Facility Information supporting the method of manufacturing in detail. An inspection of the manufacturing facility and product-specific manufacturing process, known as an on-site evaluation (OSE) is also completed to assess both the process and the facility by the Health Canada reviewers. However the OSE is not sufficient to ensure facility compliance with GMP standards, and further documentation and inspection will be needed for this (see above section on Regulation of Manufacturing Facilities).

If there is sufficient evidence to support safety, efficacy or quality claims the product is issued a notice of compliance (NOC) and a drug identification number (DIN), which allows it be sold in Canada. A notice of deficiency (NOD) may be issued where there is insufficient information that precludes a risk-benefit decision from being made; a notice of noncompliance (NON) may be issued where a decision is made that the benefits do not outweigh the risks, which the sponsor can address, typically within a 90-day period, a sponsor withdrawal. Appropriate responses to an NOD or NON can trigger a continuation of the review process, while incomplete or unsatisfactory responses will trigger a withdrawal of the submission. The submission may be refiled without prejudice [15].

A DIN is an eight-digit numerical code assigned to each drug product that is marketed in Canada, under Part C, Division 1 of the Food and Drug Act and Regulations [5]. A DIN can be used to identify the manufacturer, brand name, medicinal ingredient(s), strength, pharmaceutical form and route of administration [59].

Postmarket, Health Canada continues to maintain surveillance on the products, monitor lot releases, enforce compliance and investigate noncompliance, inspect GMP facilities and renew the EL. Health Canada provides a recall and alerts database for among other things food and health products food [56], and an adverse reaction to health products database [57]. Enactment of Vanessa's Act [51] provides additional postmarket surveillance heft to Health Canada.

Cell & gene therapeutics that have received approval by Health Canada

Only one cell therapy product, PROCHYMAL® or Remestemcel-L, adult human mesenchymal stem cells (hMSCs) has received market authorization from Health Canada. This was awarded to Osiris Therapeutics, Inc. in May 2012, under the Food and Drug Regulations. This product received conditional market authorization under the notice of compliance with conditions (NOC/c) guidance [58], and we discuss this novel approval mechanisms further below. The authorization was based on promising clinical evidence but fur-

ther confirmatory studies (in the form of a randomized clinical trial or properly conducted case control study) are needed for full market authorization by June 2016.

PROCHYMAL is approved for the treatment of pediatric, acute aGvHD that is refractory to corticosteroid or other immunosuppressive agents. It is approved for grade C or D disease in any visceral organ and for management of grade B disease in any visceral organ, except skin. At the time of approval, there were no authorized products for treating aGVHD which depending on the grade has long-term survival ranging from 80% (Grade A and B), 30% survival (Grade C) to 5% survival (Grade D).

The MSCs in the PROCHYMAL are derived from adult bone marrow that are not human leucocyte antigen matched, and are expanded in culture and cryopreserved in dimethyl sulphoxide.

Conditional approval was based on efficacy subanalysis from two clinical studies, one included 75 pediatric patients (along with adult patients), which was a single-arm study, and compared with historical controls provided by the Centre for International Blood and Marrow Research (CIBMTR) [60]; the second, a placebo-controlled trial included 28 pediatric patients. Primary endpoint was improvement in overall response (OR) of aGvHD symptoms by day 28. The placebo-controlled trial did not achieve statistical significance of its primary endpoint; however, subset analysis showed that 61–64% of refractory pediatric patients had an OR, compared with 36% in the placebo group by day 28; this trend improved further by day 100 to 77%. In the single arm study, OR was achieved by 86% of the pediatric population by day 100, compared with historical controls.

Importantly, there were no safety or infusional toxicity concerns in any of the trials with PROCHYMAL for aGvHD [60,61] including in 12 pediatric patients who received the cells under an emergency protocol [62]. There were no safety or toxicity concerns in an additional 11 nonclinical studies presented. As part of the NOC/C however, a long-term registry for follow-up of patients, and continued reporting of serious adverse events (SAEs) was recommended.

Osiris Therapeutics, Inc. had originally submitted a priority review, but received a notice of noncompliance (NON). They refiled under the NOC/C guidelines. Details summarizing this decision are publicly available [63].

An expert advisory panel (EAP) was specially convened to view the quality, safety and efficacy data of the submission and to perform a risk-benefit analysis. The severity and high mortality associated with steroid-refractory aGVHD [64,65] highlighted the urgent unmet medical need in this pediatric population. Given the safety profile of PROCHYMAL to-date, with risks generally focused on transmission of infection, and toxicology events, the EAP determined that the potential benefits outweighed the risks. Accordingly, Health Canada granted PROCHYMAL conditional market approval with the requirement to submit additional clinical trial data demonstrating efficacy, and develop a registry with long-term follow-up information.

This conditional approval process was unique to Canada at that point in time. Canada had policies in place to provide conditional market approval, and was willing to perform subset analysis of clinical trial data, which other jurisdictions do not typically perform. Since the Canadian conditional market approval, Prochymal has been approved in New Zealand, is available in the USA under the Expanded Access Program, and is approved in six other countries.

Importantly, at least in Canada, PROCHYMAL did not apply for evaluation by The Canadian Agency for Drugs and Technologies in Health upon receiving the conditional approval. Canadian Agency for Drugs and Technologies in Health is an independent, not-for-profit agency that provides formulary listing recommendations based on clinical effectiveness and cost–effectiveness of approved drugs to Canada's publicly funded drug plans (excluding Quebec). Under the conditional approval plan in Canada, sponsors can technically apply for this evaluation and can receive a recommendation to be reimbursed by the provincial plans prior to full market approval. Prochymal is yet to be reimbursed in any Canadian Province.

Process for regulatory reform & new regulations in the pipeline

Regulatory reforms engage multiple stakeholders and levels of regulation. Health Canada may promulgate regulatory reforms via policy documents, guidance documents (that provide assistance to industry and healthcare professionals on how to comply with statutes and regulations) or regulations. Amendments to legislation, primarily the Food and Drug Act, must pass through the Parliamentary process, requiring debate and majority vote in both the House of Commons and the Senate. Most recently, Parliament debated and passed Bill C-17: Protecting Canadians from Unsafe Drugs Act (Vanessa's Law), which amended the Food and Drugs Act. Changes to legislation, in turn, trigger additional regulations, accompanied by interpretive guidelines and policy documents.

Legislative changes are difficult and time consuming to implement. Often these respond to a triggering event that galvanizes political will behind the proposed reform. Vanessa's Law is an example, of such a legislative reform. It was championed by Tory member of par-

liament, Terence Young, in memory of his late daughter who died of a heart attack at age 15 while on a prescription drug for a stomach ailment, which was later pulled from the market. The law provides a new power to Health Canada to recall products and stop sales; previously, Health Canada could remove manufacturing/distribution licensure, and only provoke voluntary recalls from the manufacturers/distributors. The bill also provides Health Canada with additional oversight over products, enabling it to order postapproval tests, assessments or studies; require submission of additional information if there is serious risk of injury, and modify label or packaging if that is necessary to prevent injury. Bill C-17 received royal assent in 2014.

Regulatory reforms, however, are more commonly discussed and promulgated via new policies, guidance documents and regulations. An interdirectorate team within Health Canada, led by the Office of Policy and International Collaboration, creates new documents (policy, guidelines or regulations) for biologic drugs. Other policy offices address reforms for medical devices and pharmaceuticals and an Office of Legislative and Regulatory Modernization amends or develops regulations. Other departments offer scientific/technical, operational, clinical, safety, informational technology (IT) and other input. Draft documents may then be circulated for public/stakeholder consultation. However, some policy documents are operational and routine and are written weekly and adopted with no consultation. Generally, most guidelines and regulations are developed in collaboration with interested and affected stakeholders and are put out for public consultation, usually via publication in the Canadian Gazette (in the case of regulations) or via the Health Canada website.

Health Canada commonly seeks input from multiple stakeholders groups, including a new cell therapy stakeholder group which has national (CellCAN) and international (International Society of Cellular Therapy, ISCT) members providing regular feedback and input on policy and regulatory issues. In the past, Health Canada has participated in a workshop co-sponsored by the Stem Cell Network in December 2010, Ottawa, Ontario. The idea to create new cell therapy guidelines emerged from this workshop, which was attended by the authors and leading stem cell investigators and clinicians from Canada and other parts of the world. The workshop identified bottlenecks in translating cell-based therapies, including overly complex and uncertain regulatory pathways. Unsurprisingly, participants identified the latter as a common, global bottleneck, regardless of jurisdiction. In response to this workshop and the emerging consensus on regulatory bottlenecks, Health Canada created separate guidelines on assembling clinical trial applications for cell-based therapies; current guidelines and formats are more applicable for drugs and biologics and difficult at adapt for cell-based approaches. The new guidance document is now under revision, following a period of public comment [16]. The guidance document remains committed to Health Canada's risk/benefit analysis framework, but takes into account some of the unique characteristics of cell therapy products. It applies only to cell therapy products at the investigation stage, not gene therapy products, including cells that have been genetically manipulated for therapeutic effect. The guidance document covers three categories: chemistry, manufacturing and control (CMC) of cell therapy products, preclinical studies and clinical studies. The CMC sections include guidance on control of raw materials, reagents and excipients, on the control of human/animal-derived materials, and on process characterization and batch runs. The preclinical section includes guidance on addressing risks specific to cell therapy products including risks of tumor formation, immunogenicity, ectopic tissue formation, migration and engraftment and route of administration. The clinical section includes guidance relevant to early stage versus later stage clinical trials, on informed consent, on clinical dose, on pharmacokinetics and on assessing clinical safety and efficacy.

In between legislative reform and guidance documents are reforms to regulations, such as the proposed Orphan Drug Framework (ODF) [66]. Orphan drugs are used to treat rare disease (typically one in 100,000 people) which reduce quality of life, and place a heavy burden on caregivers and the healthcare system. The ODF is linked to Bill C-17 because it is dependent on Health Canada's authority to request additional studies and testing, and postmarket approval before the Framework can be adopted. The ODF will be incorporated into a new Division 10 of the Food and Drug Regulations; it will allow orphan drugs to be channeled into a federal regulatory pathway to improve market availability in Canada and to accelerate market authorization. Having an ODF will harmonize Canada with European and US jurisdictions that have similar special pathways for drugs that meet the orphan drug designation. Importantly, many cell- and gene-based therapies may fall under this framework as they attempt to provide treatment strategies for rare and debilitating diseases. The ODF is expected to be available for public consultation in the Canadian Gazette Part 1 in February 2015, now that Bill C-17 has received royal assent.

The Office of Policy and International Collaboration is continually seeking input from multiple stakeholders in the cell and gene therapy fields. Representatives from the Office attend pre-clinical trial application (CTA) consultation meetings to understand bottleneck issues from sponsors and investigators; they present at international meetings, for example at the

Global Regulatory Perspectives (GRP) workshop at ISCT's annual meeting. The formation of CellCAN, a national center of excellence for cell manufacturing facilities across Canada, whose mandate is to accelerate cell-based clinical trials in Canada, now provides a point group from which Health Canada can solicit input on key issues [3]; indeed CellCAN is a founding member of the cell therapy stakeholder group, a bilateral group that provides key stakeholder input to Health Canada on cell therapy related policy issues. The Office of Policy and International Collaboration is working on a gap analysis to document the disparity between current guidance documents and regulations and the evolving field of cell- and gene-based therapies. This is an important and ongoing endeavor by the regulators to keep abreast of the field and to be able to respond to a changing scientific landscape while harmonizing with international jurisdictions.

Health Canada and other jurisdictions are closely monitoring recent (November 2013) legislative changes in Japan's Pharmaceutical Affairs Law which in effect provides accelerated market approval and could help establish Japan as a global leader in regenerative medicine. Under this change (which came into effect in November 2014), a drug that completes an early stage clinical trial establishing safety and some plausible evidence of efficacy qualifies for conditional market approval. Market approval allows the drug to be available and reimbursable while garnering additional efficacy data (over a 7-year period) needed for final approval. This system could essentially allow later Phase trials to be subsidized by taxpayer dollars and represents a major shift in the current paradigm of how drugs are reimbursed and how clinical trials are funded. There is concern that decisions to reimburse started during conditional approval may be difficult to reverse if full market approval is not granted. Such questions are beginning to emerge, and are largely unanswered as jurisdictions experiment new global models for how cell therapy will be regulated and reimbursed.

This accelerated market approval process will no doubt significantly expedite the current process of drug approval (typically three or more clinical trials to establish a full profile of safety and efficacy) by a number of years. Global biotech companies are paying attention with Mesoblast, Athersys, Pluristem and Cytori having Japanese partners and investments in place to take advantage of this legislative change. Jurisdictions such as the UK are also keen to establish partnerships with Japanese researchers to take advantage of this 'crowdsourcing' opportunity to pay for expensive cell-based clinical trials and Canadian researchers and regulators will likely closely monitor developments.

While the conditional market approval is drawing a lot of attention in Japan, Canada has had a conditional approval policy in place since 1998. This NOC/c, Notice of Compliance with conditions [58] is a mechanism to allow drugs with promising clinical benefits to be available for patients with serious, life-threatening or severely debilitating diseases or conditions for which no drugs are currently marketed in Canada. It allows for a mechanism to monitor the safety and efficacy of promising drugs, postmarket and confer full approval upon completion of confirmatory trials. Essentially, the NOC/c allows for new drugs to be available to Canadian patients in the absence of full efficacy data, as long as there are promising clinical benefits accompanied by an acceptable safety profile based on benefit/risk assessment. The policy requires the sponsors to comply with restrictions that Health Canada deems appropriate for the advertising and distribution of the drug.

Prochymal was approved in 2012 under this conditional approval process, and the sponsor has until 2016 to submit an application in support of full market authorization. In Canada, like in Japan, conditional approval permits the sponsors to seek for reimbursement from provincial drug plans and others, in the absence of full market approval (the sponsors of Prochymal have not applied for such reimbursement in Canada). Questions on how this will be resolved for cell-based trials, which may or may not always receive full market authorization, are largely unanswered and untested as the community waits to see how this process will unfold in Japan and other jurisdictions, including Canada.

Conclusion

The current regulatory landscape in Canada offers a flexible, reasonable yet stringent environment which facilitates development of cell, gene and tissue-based therapies, medical devices and combination products. Indeed, Canada was the first jurisdiction in the world to conditionally approve an allogeneic stem cell product based on subset efficacy analysis of existing clinical data. The existence of a conditional approval policy, which is further strengthened by Health Canada's new postmarket monitoring authority, positions Canada globally with other nations such as Japan and the EU which are evaluating accelerated regulatory approval pathways for cell- and gene-based therapies.

Notwithstanding the current framework, there are gaps in the regulatory framework. In response, Health Canada regulators have chosen to interpret the regulations and act in a reasonable manner, typically on a case-by-case basis. The authors suggest that a case-by-case approach provides the greatest flexibility to a nascent field with a diverse range and nature of cell and gene therapy products. As the scientific and commercial field

evolves, standardized practices will emerge by consensus which the regulators can then seek to approach in a more unified manner. Encouragingly, Health Canada regulators are committed to ongoing discussions with the scientific community in Canada, and with international stakeholders with the creation of a new Cell Therapy Stakeholder group to address these gaps as the field evolves. They have put out a draft guidance document on cell therapy. The presence of a globally reputed scientific community, along with a reasonable and evolving regulatory framework makes Canada uniquely attractive in spearheading global changes to healthcare via adoption of novel cell- and gene-based therapies.

Future perspective

The next 5–10 years will be critical years as new business and regulatory models for the development, clinical investigation, regulatory approval and commercialization of cell- and gene-therapy models are being attempted globally. Much will depend on the early cell or gene-therapy products which emerge as clinical and commercial successes; their regulatory approvals process and commercialization pathways will likely set yardsticks for the field. Canada is well positioned with robust research and clinical stakeholder groups, and a flexible regulatory body to adapt to the evolving field, and emerge as a global leader.

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Executive summary

Regulations for cell therapies

- Minimally manipulated allogeneic cells, tissues and organs that meet certain criteria fall under the Cells, Tissues and Organs Regulations and do not require authorized clinical trials; they must meet various safety standards and processing facilities need to be registered and inspected.
- More than minimally manipulated cells that have systemic and/or metabolic effects are regulated as drugs under the Food and Drug Regulations, need Health Canada authorization for clinical trials and undergo a stringent approval process for market authorization.

Regulations for gene therapy products

- Gene therapy products are regulated as drugs under the Food and Drug Regulations; Canada has no specific guidance documents but follows ICH guidance documents. Glybera®, the only globally approved gene therapy product will seek market approval in Canada.

Medical devices for diagnostics/ delivery of cell or gene therapies

- Medical devices are regulated under the medical device regulations if they are sold or advertised in Canada. Intra-operative processing of cells may technically be exempt from these regulations indicating a gap in the current framework.

Regulation of manufacturing facilities

- Registration or licensure or third-party audits by approved bodies, are typically required to demonstrate GMP compliance of facilities (manufacturers and distributors) to Health Canada; the type of product and commensurate regulation dictates requirement for the manufacturing/distribution facility.

Prochymal™

- Was first approved in Canada in 2012 under a conditional market approval process, which has been in place since 1998; despite being approved, there has been no provincial reimbursement in Canada.

Process for regulatory reform & new regulations in the pipeline

- Health Canada has been and remains proactive by engaging a newly formed Cell Therapy Stakeholder group, and by putting out new draft guidelines on assembling clinical trial applications for cell-based therapies; enactment of Vanessa's Law increases Health Canada's authority postmarket, including mandating recalls; a new Orphan Drug Framework will shortly come online harmonizing Canada with other international jurisdictions.

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