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Workshop to address gaps in regulation of minimally manipulated autologous cell therapies for homologous use in Canada

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Abstract

In Canada, minimally manipulated autologous cell therapies for homologous use (MMAC-H) are either regulated under the practice of medicine, or as drugs or devices under the Food and Drugs Act, Food and Drug Regulations (F&DR) or Medical Device Regulations (MDR). Cells, Tissues and Organs (CTO) Regulations in Canada are restricted to minimally manipulated allogeneic products for homologous use. This leaves an important gap in the interpretation of existing regulations. The purposes of this workshop co-organized by the Stem Cell Network and the Centre for Commercialization of Regenerative Medicine (CCRM) were to discuss the current state of regulation of MMAC-H therapies in Canada and compare it with other regulatory jurisdictions, with the intent of providing specific policy recommendations to Health Canada. Participants came to a consensus on the need for well-defined common terminology between regulators and stakeholders, a common source of confusion and misinformation. A need for a harmonized national approach to oversight of facilities providing MMAC-H therapies based on existing standards, such as Canadian Standards Association (CSA), was also voiced. Facilities providing MMAC-H therapies should also participate in collection of long-term data to ensure patient safety and efficacy of therapies. Harmonization across provinces of the procedures and practices involving administration of MMAC-H would be preferred. Participants felt that devices used to process MMAC-H are adequately regulated under existing MDR. Overly prescriptive regulation will stifle innovation, whereas insufficient regulation might allow unsafe or ineffective therapies to be offered. Until a clear, balanced and explicit approach is articulated, regulatory uncertainty remains a barrier.

Key Words: *autologous cell therapy, Canada, minimal manipulation, policy, registration, regulation, standards, stem cell tourism*

Introduction

The regulatory approach taken for autologous cell therapies is dictated, in part, by the intended clinical use of the cells and the specifics of their processing. In some cases, particularly in the cosmetic and orthopedic sectors, harvested cells undergo minimal manipulation and are returned to the same patient. In most jurisdictions, minimal manipulation is defined as acts that do not result in fundamental changes to the structure or biological characteristics of the original cell or tissue (definitions from different jurisdictions are provided in Supplementary Table SI). Minimally manipulated autologous cell therapies for homologous use (MMAC-H) therapies are typically not regulated in the same manner as their more-than-manipulated or non-homologous counterparts. Health Canada defines "homologous use" as a cell, tissue or organ performing the same basic function after transplantation (definitions of homologous use in different jurisdictions are provided in Supplementary Table SII).

MMAC-H therapies in Canada may be regulated as a drug under Food & Drug Regulations (F&DR), a device that is advertised or sold to process the MMAC-H therapy may be regulated as a medical device under Medical Devices Regulations (MDR) and the administration of the MMAC-H therapy falls under provincial practice of medicine. Other regulations (The Safety of Human Cells, Tissues and Organs for Transplantation Regulations and Blood Regulations) do not

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apply, but may help inform how MMAC-H therapies could be regulated. However, uncertainty remains in the application and interpretation of these multiple regulations. There are no policies explicitly written to address cell products that are autologous, minimally manipulated, intended for homologous use and without a systemic effect in Canada, in contrast with other jurisdictions such as the United States and Australia where there are existing explicit regulations and these issues are being revisited by regulators through the issuance of draft guidance documents [1,2] and public regulatory consultations [3] .

There has been consistent growth in the number of autologous cell therapy studies advancing into clinical trials in Canada. As of August 2016, approximately 41 cell therapy trials were ongoing, enrolling or planned in Canada, 46% of which were using autologous cell therapies [4]. There are also intense commercialization efforts underway, underscored by the global market value of autologous cell therapies, estimated to be US $4.87 billion in 2016 and poised to reach US $23.75 billion by 2024 [5]. In a recent audit of direct-to-market stem cell therapies, Berger *et al.* identified six unique websites advertising stem cell–based therapies in Canada [6]. Using a series of structured online searches, we identified 11 such websites advertising clinics offering cell therapies in Canada [4]. The discrepancy in our findings and those of Berger *et al.* is likely accounted for by differences in search strategy and stringency the year in which the search was conducted (2016 versus 2017). Eight of the 11 clinic websites that were reported offered autologous treatments for orthopedic (4/8) and cosmetic (4/8) indications, whereas the remaining three websites did not provide sufficient detail on cell harvesting procedures to be able to conclude if autologous or allogeneic cells were being marketed. This trend of stem cell clinics taking advantage of real or perceived gaps in regulation is not restricted to Canada. For example, in the United States, there are an estimated 351 businesses operating 570 clinics that offer autologous cell therapies, many of which are unregulated [7]. Although no serious complications in recipients of unregulated cell therapy treatments have yet been reported in Canada, elsewhere cases of meningitis [8], brain and spinal tumors [9] and angiomyeloproliferative lesions [10] have occurred. More recently, three women suffered severe, permanent bilateral eye damage after receiving intravitreal injections of autologous, adipose-derived stem cells in the United States [11], and in Australia the death of a patient who had received an autologous treatment resulted in a coroner's inquest [12]. These examples highlight the inherent dangers of using unregulated, unproven therapies and provide rationale for pre-emptive regulatory reform in Canada.

Given the increased trend of direct-to-consumer marketing of unproven, potentially unsafe cell therapies, the lack of policies categorically addressing MMAC-H therapies in Canada and the upcoming review cycle of Cells, Tissues and Organs (CTO) guidelines by Health Canada in 2018, we considered it timely to discuss the state of regulation of MMAC-H therapies in Canada. To discuss these challenges and potentially propose regulatory reform, representatives from regulatory agencies, academia and industry and clinicians convened on March 8, 2017 in Montréal, QC, Canada for the "Gaps in cell therapy regulation—Where to fit minimally-manipulated cell-based therapies and related processing devices?" workshop. The first half of the 1-day workshop focused on an overview of the Canadian as well as the United States and European Union (EU) regulatory landscapes to provide context to inform the workshop discussions. Presentations were given by domestic and international experts. The second half of the workshop consisted of guided discussion and formulation of policy recommendations for Canadian regulators based on a general consensus of workshop attendees.

Thirty-four invited participants attended the workshop (Table I) and included academic researchers, Good Manufacturing Practice (GMP) technicians, clinicians, ethicists, legal professionals, regulatory professionals, device manufacturers, members of the biotechnology industry, cord blood processing professionals and blood services professionals from across Canada. To assess attendees' experience, familiarity and views of regulation of MMAC-H therapies in Canada, participants were asked to complete a short survey prior to the workshop. Of the 34 participants, 26 responded; 57.7% of respondents self-identified as being either directly or indirectly involved in processing or providing MMAC-H therapies for patients (Figure 1A); 46.2% felt that MMAC therapies are not consistently regulated in Canada, whereas 30% felt they are (Figure 1B); half of the respondents believed that Health Canada should change how it regulates MMAC-H therapies, whereas merely 14% believed regulation should remain the same (Figure 1C).

The workshop focused on the following areas: (i) providing a range of Canadian perspectives on the regulatory constraints of translating MMAC-H therapies to the clinic to identify areas where regulatory approaches converge or differ between US, European, Australian and Canadian jurisdictions and (ii) discussing the approaches leading to potential recommendations on changes to the existing regulatory framework in Canada. This report is intended to reflect the discussion and general consensus from the workshop and not necessarily the views held or expressed by all individual participants (or co-authors) or their organizations.