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Meeting report

The regulation of cell therapy products in Canada

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ABSTRACT

This article provides a high level view of how cell therapy products are regulated in Canada and addresses the regulatory framework, pathways and underlying regulatory authority. The regulatory approach involves, primarily, two major sets of regulations; and the scientific basis for product categorization and the application of each of these pathways is discussed. Products that undergo more than minimal levels of processing, or meet certain other criteria, are regulated as biological drugs under the applicable parts of the *Food and Drug Regulations*. Other cellular products, primarily those for allogeneic transplantation and with an established therapeutic use, are regulated under the more recently promulgated *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*, which incorporate a standards-based approach. Various concerns and challenges for these classes of products are discussed and information is provided on current sources of relevant guidance, including specific Health Canada guidance currently being developed. Health Canada strongly supports and participates in efforts aimed at international regulatory convergence and harmonization.

1. Introduction

This is a short article focused on high-level aspects of the Canadian regulatory framework and approach to cell therapies; and is based on a scientific meeting presentation. Some issues were addressed in more detail in additional presentations.

Cell Therapies are clinical interventions designed to treat disease or medical conditions by modifying biological processes in human subjects. The aim of regulatory oversight is to protect treatment subjects and to help assure all stakeholders, and the broader public, that the processes used to procure, process and administer cells meet appropriate standards such as Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Clinical Practice (GCP), and encompass ethical principles; and that medicinal claims are proven through data collected according to proven scientific and clinical methodologies. A key objective of National Regulatory Authorities, including Health Canada, is for stem cells and somatic cells to be safe and meet the highest quality standards.

In addressing this topic from a Canadian perspective, this article covers:

- Regulatory responsibility and mandate;
- Regulatory Framework and authority;
- Regulatory pathways and product categorization;
  - Overt regulation of cell therapies as biological drugs;
  - Standards-based regulation of allogeneic transplantation;
- Guidance relevant to cell therapy products;
- International harmonization and convergence.

There have been a limited number of cellular therapy products to reach marketing approval internationally, however, the great steps forward in the isolation and directed differentiation of stem cells holds great promise for many new products. The first stem cell product to obtain a marketing approval was Prochymal (remestemcel-L), from Health Canada on May 17, 2012. Prochymal is a population of adult mesenchymal stem cells for IV infusion in the

Abbreviations: AHR Act, *Assisted Human Reproduction Act of Canada*; BGTD, Biologics and Genetic Therapies Directorate; CBER, Center for Biologics Evaluation and Research; CDER, Center for Drugs Evaluation and Research; CHMP, Committee for Medicinal Products for Human Use; CIHR, Canadian Institutes of Health Research; *CTO Regulations*, *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*; EMA, European Medicines Agency; *F&D Act*, Canadian *Food and Drugs Act*; *F&D Regulations*, Canadian *Food and Drug Regulations*; FDA, United States Food and Drug Administration; GMP, Good Manufacturing Practice; HPFB, Health Products and Food Branch; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; NSERC, National Science and Engineering Research Council; SSHRC, Social Science and Humanities Research Council; USP, United States Pharmacopoeia.

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management of acute graft-versus-host disease and has since been approved in several regulatory jurisdictions.

2. Regulatory responsibility and mandate

Within Health Canada, responsibility for cell therapy products falls to the Biologics and Genetic Therapies Directorate (BGTD) which forms part of the Health Products and Foods Branch (HPFB). BGTD regulates all biological drug products (and so has a mandate somewhat analogous to the US FDA's CBER before the transfer of specified recombinant products to CDER). Other Directorates within the Branch are responsible for: prescription chemical drug products and devices; non-prescription drug products and natural health products; and food. (In a Canadian government department, a "Branch" is a higher level structure, and a "Centre" or "Bureau" is a lower level structure, in comparison to the organizational structure of the US Department of Health and FDA).

The core activities of biologics oversight and evaluation are conducted in two Centres within BGTD, with responsibility for cell therapy products being shared. The Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics (CERB) has product responsibility that includes gene therapies and therapeutic somatic cell therapies, including immune therapies. The Centre for Biologics Evaluation (CBE) has product responsibility that includes cells and tissues for transplantation (repair and replacement) including more traditional and new stem cell approaches; and recombinant vectors, including cells, designed to display epitopes for the generation of a prophylactic immune response.

3. Regulatory framework

Canadian regulatory frameworks are comprised of various elements: Statutes, or Acts, provide scope, high-level principles, and the legal authority to make regulations; Regulations interpret the Acts and provide general details on what must be done; Guidelines interpret and provide details of how to meet the regulations - being faster and simpler to introduce (because they are not legally binding), they allow flexibility and adaptation to change; Policies expand or modify the interpretation of regulations - they usually relax or simplify, providing a "quick fix" pending re-drafting of regulations; and all have a role to play in the regulation of cell therapies.

There is no formal Canadian regulatory definition of cell therapy; and cell therapies are not specifically listed on *Schedule D* to the *Food and Drugs Act* (*F&D Act*) which identifies biologics, and which brings to bear a specific set of regulations under *Part C, Division 4 of the Food and Drug Regulations* (*F&D Regulations*). Nevertheless, some types of cell therapy products are captured by class listings on *Schedule D* and so, logically, and in step with other regulatory jurisdictions, many cell therapies are regulated as biologics. As part of ongoing regulatory modernization, the biologic status of cell therapy drugs will be addressed by changes to *Schedule D* or by other means.

A different regulatory approach is taken for organs and minimally manipulated cells and tissues that are intended for allogeneic, homologous use, which does not involve the pre-market evaluation of a New Drug Submission.

Therefore, the regulatory approach to cell therapy products involves two major categorizations supported, primarily, by two sets of regulations. There is overt regulatory oversight for cell therapy drug products governed by longstanding and widely applicable parts of the *F&D Regulations*; and a standards-based regulatory approach to allogeneic transplantation governed by the more recently developed *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (*CTO Regulations*).

Cell therapy products and medical device products whose components are integrated into a singular product are regulated as combination products (e.g., cells that are encapsulated or grown on a non-living scaffold). Where the principal mechanism of action for the claimed effect or purpose is achieved by pharmacological, immunological or metabolic means, the *F&D Regulations* apply. In certain other circumstances, such as where the function or goal is structural, the Medical Device Regulations may apply. The HPFB Therapeutic Products Classification Committee may be engaged to reach a final decision regarding classification; however, regardless of the outcome, appropriate expertise from across the HPFB is used to assess combination products. The evaluation of medical devices is beyond the scope of this short article.

In addition, certain provisions of the *Assisted Human Reproduction Act of Canada (AHR Act)* will apply to embryonic stem cells. The creation of an embryo for any purpose other than for reproduction is prohibited in Canada; however, "leftover" embryos can be used for research with appropriate consent.

The *AHR Act* provides for the creation of a licensing framework which, if established, would cover all private and public research involving the use of human in vitro embryos, including the derivation of stem cell lines. However, the regulatory framework would not extend to research on existing stem cell lines, or beyond the point of derivation of new stem cell lines.

4. Regulatory pathways and associated regulations

Cell therapy products that undergo manufacturing, where processing involves more than minimal manipulation, or that meet other specific criteria, are regulated as biological drugs. As a large class of products, biologics present specific regulatory challenges compared to chemically-synthesized drugs. There are: risks associated with starting materials and with adventitious agents during manufacturing; the inherent variability of products derived from processes that use living systems; and, difficulty in precisely controlling manufacturing, processing and implanting. It is often stated that for biologics, processing defines the characteristics of the product; and this is particularly valid for cell therapy products. Additionally for cellular products, it may take a long time to see the results of treatment, either benefits or risks; and treatment cannot be withdrawn in response to an adverse event.

Regulatory requirements are defined within *Part C, Divisions 1A* (Establishment Licensing), *2* (GMP), *4* (Biologics), *5* (Clinical Trial Applications) and *8* (New Drugs) of the Canadian *F&D Regulations*. Through the application of *Division 4* (Biologics), these products are subject to On-Site Evaluation of manufacturing sites and the testing of consistency lots as part of the pre-marketing evaluation process (both discretionary), and to the Lot-by-lot Release Program. The Lot-by-lot Release Program can incorporate suitably modified approaches to reflect the small, or even single-treatment, lot sizes, and the reality of retrospective safety testing for some rapidly used products. Guidances and policies relating to Biologics also apply, as do the target time frames for drug review.

Some cellular therapies that meet certain criteria and that have an established therapeutic use may be subjected to a less stringent, regulatory approach under the *CTO Regulations*. These regulations came into force in December, 2007, with the purpose of minimizing the potential health risks to Canadian recipients of human cells, tissues and organs (e.g., transmissible diseases). The focus is on activities performed by "source establishments", for example: cell and tissue banks, transplant establishments, organ donor organizations and organ procurement organizations. The regulations are standard-based and directly reference certain sections of the Canadian Standards Association (CSA) that are related to the safety of