Regulation of Cell Therapy Products: Something Different and Something New

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Risk Based Approach:
Oversight aligned with risk of product or activity

Food and Drugs Act

Food and Drug Regulations

Safety of Human Cells, Tissues and Organs for Transplantation Regulations (2007)

Cells considered “drugs”
- Requirement of pre-market approval; Establishment License; Good Manufacturing Practices; Lot Release testing; and Supporting Evidence of Safety, Quality, and Efficacy

Investigational Cells
- Requirement of authorization to perform clinical trial

Cells for transplantation
- Requirement to certify the establishment is in compliance and that the cell is safe for transplantation

Something New
- New Drug Submission
- Clinical Trial Application
- Establishment Registration
Safety of Human Cells, Tissues and Organs for Transplantation Regulations

- **Scope:**
  - Applies to organs and minimally manipulated cells and tissues:
  - Intended for allogeneic, homologous use

- **Prohibition:**
  - No establishment shall transplant CTO unless they have been processed by a registered establishment; and
  - determined safe* for transplant
    - Except under the provision of Exceptional Distribution

*Safe = processed in accordance with the Regulations
CTO Regulations

• Purpose: Minimize the potential health risks to Canadian recipients of human CTO
• Balance the need for safe CTO with the need to ensure availability of CTO for transplantation

• Standard-Based Regulations: Canadian Standard Association (CSA)
  • The CTO Regulations directly reference certain sections of the CSA that are specific to the safety of CTO
  • Donor screening, testing and suitability assessment
Why a Standards-Based Approach?

• Can respond more effectively and rapidly to changes in science and technology
  • easier to update than regulations
• Can improve compliance via a consensus approach to development
• Can facilitate international harmonization, if done through recognized standards writing organization
• Uses a balanced representation of stakeholders in development process
• Written in non-legal/regulatory language
Developing National Standards

In order for a standard to be recognized as a National Standard in Canada it must:
• Be developed through a consensus process
• Includes a public review period
• Be developed by an accredited standards writing body
• Be consistent with or incorporate existing international standards
• Not be written to serve as a barrier to trade or to limit innovation or freedom
• Be available in both official languages
Standard-Based Regulations

- Although numerous sets of standards existed, there was no one pre-existing standard that met Canadian needs and could be adopted, even with modifications.
- Health Canada contracted the Canadian Standards Association (CSA)
  - (CSA) Z900 Series
    - Z900.1 CTO for Transplantation: General Requirements
    - Z900.2.2 Tissues for Transplantation;
    - Z900.2.3 Perfusable Organs for Transplantation;
    - Z900.2.4 Ocular Tissues for Transplantation; and
    - Z900.2.5 Lymphohematopoietic Cells for Transplantation.

- 1\textsuperscript{st} Edition – August 2003
- 2\textsuperscript{nd} Edition – December 2012
Request / Evaluation / Authorization

Preliminary Stage: Request is received, an evaluation conducted and the project submitted for authorization.

Assign to Committee

Proposal Stage: Technical committee is formed (if an appropriate one does not exist) and a Notice of Intent to proceed is issued.

Notice of intent

Meeting / Draft

Preparatory & Committee Stages: Working draft prepared, project schedule established and Technical Committee meets to develop /refine draft.

Public Review

Technical Committee consensus

Enquiry Stage: Draft is offered for public review and comment after which CSA staff conduct a quality review and a preapproval edit is completed.

Internal review (Quality / preapproval edit)

Technical content approval

Procedural approval

Approval Stage: Technical Committee approves technical content (by formal vote) and a second review confirms that procedures were followed.

Final edit / publication

Dissemination

Publication Stage: CSA staff conduct a final edit and verify conformity with editorial and procedural guidelines, then the standard is published.

Maintenance

Maintenance Stage: The standard is maintained to keep it up to date and technically valid.
Standard-Based Regulations

• Standards are made mandatory only when they are incorporated by reference into government regulations

• Health Canada can only use sections of the standards that are:
  • under federal authority
  • absolute requirements

• The CTO Regulations use an “ambulatory” reference
  • An amendment to a referenced section of the Standard automatically changes the regulatory requirement
Donor Suitability Assessment

S.18: “In assessing the suitability of a donor of cells, tissues or organs...an establishment must perform the following steps:

... determine that the donor is not unsuitable to donate on the basis of the contraindications or exclusion criteria set out in section 13.1.3 of the general standard and in Annex E to that standard”

Annex E
Exclusionary Criteria for Human Immunodeficiency Virus (HIV) Risk Behaviours

Note: This Annex is a mandatory part of this Standard.

E.1
The exclusionary criteria for human immunodeficiency virus (HIV) risk behaviours shall be as follows:

a) men who have had sex with another man in the preceding five years;

b) persons who report nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding five years;

c) persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates;

d) men and women who have engaged in sex in exchange for money or drugs in the preceding five years;

e) persons who have had sex in the preceding 12 months with any persons described in Items a) to d) or with a person known or suspected to have HIV infection;

f) persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, nonintact skin, or mucous membrane; and

g) inmates of correctional systems (because of difficulties with informed consent and increased prevalence of HIV in this population).

13.1.3
It is recognized that contraindications or exclusion criteria will vary between cells, tissues, and organs as defined in the specific subset Standards. Examples of contraindications or exclusion criteria include, but are not limited to,

a) death from an unknown cause;

b) death with neurological disease of an unestablished etiology (e.g., Alzheimer’s, multiple sclerosis, Parkinson’s, amyotrophic lateral sclerosis (ALS));

c) prion-related disease (e.g., Creutzfeldt-Jakob disease (CJD), family history of CJD, recipients of human-derived pituitary growth hormone or dura mater);

d) subacute sclerosing panencephalitis;

e) progressive multifocal leukoencephalopathy;

f) rabies;

g) high risk for human immunodeficiency virus (HIV)

Note: See Annex E for guidelines for preventing the transmission of HIV.

h) persons with repeatedly reactive screening assays or who test positive for

i) antibody to HIV types 1 or 2 (anti-HIV-1 or anti-HIV-2);

ii) hepatitis B virus surface antigen (HBsAg);

iii) antibody to hepatitis C virus (anti-HCV); or

iv) antibody to human T-cell lymphotropic virus types I or II (anti-HTLV-I or anti-HTLV-II);

j) active systemic bacterial, fungal, or viral infection; and

k) leukemias and lymphomas.
NOC/c issued for Prochymal, May 17, 2012
NOC/c Policy

1.2 Policy Statement

A Notice of Compliance issued under the NOC/c policy may be granted for a drug product with promising clinical benefit, providing that it possesses an acceptable safety profile based on a benefit/risk assessment, and is found to be of high quality.

Prior to authorization, the sponsor must submit a “Letter of Undertaking” acceptable to Health Canada which includes:

1) Sponsors of an NDS or SNDS must undertake to design, carry out and report on well designed confirmatory trials to verify the clinical benefit of the drug. The sponsor must undertake to carry out any such trials in accordance with established scientific standards.

2) Sponsors of an ANDS or SANDS that references a Canadian Reference Product (CRP) with NOC/c indications, must undertake to design, carry out and report on well designed confirmatory trials to verify the clinical benefit of the drug, if deemed necessary given the status of the molecule.

3) All sponsors must undertake to pursue enhanced post-market monitoring and report on the safety and effectiveness of the drug product.

4) All sponsors must clearly reflect and highlight the conditions under which the drug product is authorized in the Product Monograph, the Consumer Information Section and/or the labelling for that product.

5) The sponsor may be requested for an undertaking to comply with restrictions deemed appropriate by Health Canada on the advertising and distribution of the drug product.
Prochymal (remestemcel-L)

• adult human mesenchymal stem cells (hMSCs) for IV infusion
  • hMSCs can mitigate autoimmune diseases caused by T-cells
• indicated in the management of aGvHD (Grade C&D) in paediatric patients
  • in cases where aGvHD is resistant to treatment with systemic corticosteroid therapy and/or other immunosuppressive agents

Acute Graft versus Host Disease (aGvHD)

• progressive, debilitating, and lethal complication of bone marrow and haematopoietic stem cell transplantation
  • involves a reaction of donor immune cells against host tissues
• represents largest component of transplant-related mortality
Evidence of efficacy from two clinical trials

1. Phase II Single-arm, multi-centre, 75 paediatric patients
   • In patients with Grade B to D aGvHD and failed response to steroid treatment or other therapies
   • Efficacy determined by Complete Response or Partial Response at day 28 day 100 post-1\textsuperscript{st} infusion
   • Statistically significant improvement at both times

2. Phase III, randomised, double-blind, placebo-controlled, 216 adult & 28 paediatric patients
   • In patients with Grade B to D aGvHD and failed response to steroid
   • Efficacy determined when results from Phase II study combined with results from this study
   • Statistically significant at both day 28 and day 100 (when using additional data)
Summary: Scientific & Regulatory Basis for Decision

- Only preliminary evidence exists to indicate a potential therapeutic value for Prochymal; however, Prochymal has not exhibited worrisome toxicity and has shown a relatively benign safety profile.

- Support from Expert Advisory Panel.

- HC considers that the benefit/risk profile is favourable for the approved indication but has required as part of the market authorisation:
  - Risk Management Plan
  - Post-market confirmatory studies
  - Registry of treated patients
  - Distribution limited to experts at paediatric blood/marrow transplant centres
Summary Basis of Decision (SBD) for PROCHYMAL®

Contact: Office of Regulatory Affairs, Biologics and Genetic Therapies Directorate

PROCHYMAL®
Remestemcel-L, Adult Human Mesenchymal Stem Cells (hMSCs)
100 × 10^6 hMSCs per 15 mL, cell suspension
Osiris Therapeutics, Inc.
Submission Control Number: 150026
Date Issued: 2012/10/05

Thank you!

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