Regulation of Cell Therapy Products in Canada

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The opinions expressed in this presentation are those of the presenter and do not necessarily reflect those of the Government of Canada.

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Canada

Population (2011): 33.5 million
Life Expectancy (2009): male: 79 years / female: 83 years
Age Profile (2011):
0-14 16.7%
15-64 68.5%
65+ 14.8%
Centenarians: 100+ 4,870 females 955 males
Languages (2006): English 58.3%, French 22.3%, other 20.5%
Health Canada: Breakdown of Departments

Key Groups currently involved with Cell Therapy Products

- Office of Policy and International Collaboration
- Centre for Blood and Tissue Evaluation
- Centre for Evaluation of Radiopharmaceuticals and Biotherapeutics
- Centre for Vaccines Evaluation
- Office of Policy and International Collaboration
- Evaluation of Cell Therapy Products Involving Scaffolds
- Evaluation of Cell Therapy Products Involving gene therapy
- Cell Therapy Research Program & Biostatistics Program

Stakeholder Interactions
Policy/Regulatory Advice-Development
Evaluation of Cell Therapy Products

Minister of Health
Deputy Minister
Associate Deputy Minister
PHAC
CIHR

Biologics and Genetic Therapies Directorate
Health Products and Food Branch
Therapeutic Products Directorate
Medical Devices Bureau
Products or therapies containing human cells that have been more than minimally manipulated and/or are intended for non-homologous use.
What are Cell Therapy Products?

Examples

- **Stem cells** of all types (i.e. somatic (SSC), induced pluripotent (iPSC) or embryonic (ESC))
- Any **cell, tissue or organ derived from stem cells** through experimental manipulation
- **Progenitor cells** or more **differentiated cell types** (e.g. endothelial progenitors, fibroblasts, epithelial cells)
- **Autologous** or **allogeneic** cells
- Cells derived from the **embryo, foetus** or any stage of human development from **neonate to adult**
- Cells that have undergone **genetic manipulation**
What are not Cell Therapy Products?

Products containing human cells but NOT considered Cell Therapy Products

- Blood components for transfusion
- Xenotransplantation products
- Allogeneic tissues, cells and organs for homologous transplantation applying methods extensively proven as safe and efficacious
- Gametes/embryos used for assisted reproduction
Regulatory oversight provides assurance for subjects and the broader public that Cell Therapies meet specific standards:

- GLP, GMP and GCP standards applied for preclinical studies, product manufacturing and clinical trials
- Tissue procurement and clinical trials adhere to proper ethical principles
- Enough evidence on the medicinal claims and the acceptability of product safety profile have been obtained and assessed through appropriate scientific and clinical methodologies

Health Canada’s goal is to provide Canadians access to products with a highly favorable risk benefit profile.
Regulation of Cell Therapy Products

Health Canada’s Regulatory Role

- Authority: *Food and Drugs Act (FDA)*
- Regulations: *Food and Drug Regulations (FDR)*

Part C: Drugs
- Division 1 - General Requirements
- Division 1A - Establishment Licensing
- Division 2 - Good Manufacturing Practices
  - Annex to the GMP Guidelines, GMPs for Biologics
- Division 4 - Schedule D (Biologic) Drugs
- Division 5 - Clinical Trial Applications
- Division 8 - New Drugs
Interpretation of Food and Drug Regulations

Food and Drug Regulations

1. A regulatory framework.
2. Generally applicable to all types of drugs.
3. Legally binding
4. Should allow the regulation of new and emerging drugs

Regulatory Guidance!
Health Canada-Stakeholder Interactions

- Stem Cell Network Meeting-Montreal, 2010
- Workshop on Global Harmonization for Stem Cell Based Clinical Trial Evaluation-ISSCR, 2010
- WHO Expert Committee on Biologic Standards-Geneva, 2011

Need for Guidance regarding:

a) Pre-clinical studies
b) Clinical trial applications
c) Quality and Manufacturing requirements
1. Consult existing quality, pre-clinical, and clinical drug product development guidance
   - ICH, FDA, EMA, HC
2. Incorporate knowledge gained from HC’s own Cell Therapy Product regulatory experience (Clinical Trials and Prochymal NDS)
3. Prepare Draft outlines for internal/external consultations
4. International collaboration and convergence (WHO)

Harmonized approach that incorporates the experience of both regulatory authorities and stakeholders
Quality and Manufacturing regulatory challenges

- Risks associated with **starting materials** or **adventitious agents**
  - donor tissues (virus transmission)
  - excipients of animal or human origin (serum, plasma)
  - non-GMP grade materials

- Product specifications: High level of **variability** expected.

- Limitations due to **sample size**.

- Product **stability**.

- Issues associated with **autologous products**:
  - introduction of adventitious agents/ cross contamination
  - limited materials (reduced options for process control)
  - developing specifications

- “Processing defines the characteristics of the product”
Challenges & Regulatory Concerns – Clinical

- **Risk assessment issues:**
  - Tumour formation
  - Ectopic tissue formation
  - Biodistribution and engraftment
  - Immunogenicity
  - Route of administration
  - Gene transfer
  - Duration of safety follow-up

- **Benefit assessment issues:**
  - Limitations of pre-clinical models
  - Difficulty in determining mechanism
  - Defining clinical dose
  - Small trials in rare indications
General Concerns

- Stem Cell Tourism
- Ethical/safety considerations for donors
- Moving too quickly to the clinic can set back the field
- Are we enabling the access to / marketing of good quality Cell Therapy Products?
- Quality (manufacturing) and Clinical components.

- Format adopted by ICH and previous HC Biologics guidance documents.

- Particular emphasis on novel aspects of Cell Therapy Products.
Common Technical Document (CTD)

CTD Triangle

The CTD triangle. The Common Technical Document is organized into five modules. Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions.

Quality Information:

- Common Technical Document (CTD) Format consistent with ICH.
- Outlines minimal quality expectations for:
  a) donor cell and tissues
  b) materials used in manufacturing
  c) drug substance, excipients and drug product
  d) container closure systems
  e) equipment and facilities
- Outlines quality control and product specification information that is expected for New Drug Submissions.

It is expected that quality controls and specifications are continually introduced during drug development based on data obtained during pre-clinical and clinical phases.
Manufacturing Process Steps

- **Drug Substance (DS):** An intermediate that arises from a clear stopping point in the manufacturing process and must meet specific pre-defined quality criteria to be useful for product development.

- **Drug Product (DP):** The final cell preparation that is intended for administration to the patient. DP manufacturing could involve further manipulation of DS (i.e., culturing), or formulation of DS.
Quality Information to be included in CTD

a) **Donor screening** methods (e.g., general health, infectious disease testing, karyology).

b) **Source and proof of safety** for **animal/human derived materials** (e.g., serum, cytokines, plasma).

c) **Specifications** for evaluation of product quality (e.g., viability, surface marker expression) and justification of specifications.

d) Details of the individual steps of the manufacturing process.

e) Validated analytical methods for product characterization and quality control.
Quality Information to be included in CTD (cont.)

e) **Sterility testing** should be completed on:
   1. Drug substance.
   2. Drug product.
   3. Reusable equipment.

f) **Stability** of the Drug Substance and Product must be determined following:
   1. Storage
   2. Shipping

g) Adventitious agent testing should be performed where applicable

h) Safety and compatibility of container closure system
Qualification and Control of Ancillary Materials

- A list of ancillary materials must be provided
- Materials should be USP or cGMP grade whenever possible
- Quality control tests should be developed or adopted for each material.
  - Identity
  - Purity
  - Sterility
  - Functionality
- Pre-clinical evidence that the levels of ancillary materials remaining in the final product present minimal risk
Overall, quality submission information should provide **sufficient scientific evidence** that the manufacturing process develops a product that is **safe for use in humans**.
Pre-clinical and Clinical Information:

- Pre-clinical studies (GLP standards, animal models, etc.)
  - Support further product clinical development
- Clinical study design
- Ethical expectations and standards
- Data analysis
- Clinical monitoring expectations.
  - length of the follow-up (efficacy and safety)
  - enhanced adverse event monitoring
- Risk mitigation and risk management strategies
The Cell Therapy Product Guidelines are intended to supplement previous HC documents:

- Guidance for Industry: Good Clinical Practice
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications

AND adhere to ICH principles outlined in:

- ICH E2F: Development Safety Update Report
- ICH E6: Good Clinical Practice
- ICH E8: General Considerations for Clinical Trials
- ICH E9: Statistical Principles for Clinical Trials
- ICH E10: Choice of Control Group and Related Issues in Clinical Trials

Sponsors should consult these documents prior to planning clinical trials and preparing regulatory applications.
Pre-Clinical Studies

Must be designed to ensure adequate risk benefit balance to allow and support further clinical development.

Assessment of Risk:
- Tumour formation
- Immunogenicity
- Reproductive effects
- Ectopic tissue formation
- Cardio-pulmonary effects
- Long-term effects
- Biodistribution and engraftment
- Administration effects

Assessment of Benefit:
- Rationale for choice of experimental model(s)
- Duration of effect
- Reproducibility of effect
- Mechanism of effect
- Dose relationships

Each product has an inherent risk benefit profile!
Pre-Clinical Models

Appropriateness of experimental model depends on:

- **Anticipated risks** associated with product.
  - high risk products require more extensive testing

- **Availability** of model systems.
  - disease models may yet to be developed
  - multiple models (which is superior?)

- Route of **administration**.
  - should simulate clinical delivery as closely as possible
  - large animal models may be most appropriate

- **Relevance** to human situation.
  - disease mechanism
  - xenogeneic considerations

The rationale for the choice must be provided!
Clinical Issues Specific to Cell Therapy Products

1. **Ethical guidelines** for protecting rights of both tissue donors and trial participants.
   - CIHR Stem Cell Oversight Committee Guidelines must be followed

2. Traditional **Phase I trials** in normal adults are often not appropriate.
   - Initial studies Phase Ib/II to evaluate safety and tolerable dose in appropriate indication

3. Longer **follow-up periods** for safety and efficacy monitoring.
   - Potential life-long follow-up for certain products.

4. Difficult to predict and determine **clinical dose** range from pre-clinical data.
   - Careful planning of clinical trials will be critical to determine beneficial dose.
   - Maximum tolerable dose may be dependent upon route of administration.
A Risk Management Plan (RMP) / Risk Evaluation and Mitigation Strategies (REMS) must be submitted when seeking product marketing approval.

- Safety Profile: Outlines all the risk information accumulated on the product (all dosage forms & strengths) during its global use in humans:
  - clinical trials
  - expanded (exceptional) access
  - off label use
  - marketed (approved/licensed) use
  - studies included in the risk minimization strategy
- Safety surveillance plan (i.e. gathering of additional safety information)
- Risk minimisation activities
- Monitoring the efficacy of the proposed plan and activities above

The planning and development of the RMP/REMS must be fully integrated into early and throughout all the phases of the clinical product development.
Proper risk-benefit analysis must still be completed on products intended for treating rare indications.

Dialogue between the sponsor and Health Canada is strongly recommended to discuss specific issues relating to clinical investigation of these products. (i.e. several pre-CTA meetings)
Guidance Development – The Way Forward

1. Consult existing pre-clinical, clinical and quality guidance.

2. Incorporate knowledge gained from previous Cell Therapy Product submissions (CTA and Prochymal NDS)

3. Draft outline for internal consultation. **Current Stage**

4. Draft for external consultation
Scientific/Clinical/Technical Issues:
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Muchas Gracias!

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The End