Navigating federal regulatory pathways for cell therapy products

OIRM Clinical Trials Initiative Workshop
May 10, 2016
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Purpose

• To provide you a practical orientation to the federal regulatory landscape for cell therapy researchers
• To identify tools / provide advice that may help you
• To address FAQs and provide context for Q&As
• To hear about your regulatory challenges / needs
Overview

1. Groups at Health Canada and their roles
2. Canadian (federal) regulations and processes
3. Guidance for cell therapy clinical trial sponsors
4. International approaches & harmonization tools
5. Tips and tools for navigating regulatory interactions
6. Frequent Asked Questions (and responses!)
7. Discussion
Health Products and Food Branch

- minimize health risk factors to Canadians while maximizing the safety provided by the regulatory system for health products and food; and,
- promote conditions that enable Canadians to make healthy choices and providing information so that they can make informed decisions about their health

Note – Health Canada’s organizational chart has not yet been revised to reflect reorganization/renaming of Regions and Programs Branch
A closer look at the Branch

Health Products and Food Branch

Therapeutic Products Directorate

Medical Devices Bureau

Biologics and Genetic Therapies

Office of Policy and Int’l Collab.

Office of Regulatory Affairs

Centre for Biologics Eval

Centre for Eval of Radiopharm and Biother

Note: Incomplete org chart intended for basic orientation to certain groups
**Food and Drugs Act**

**Basis:** Constitutional criminal law powers

**Purpose:** to prevent fraud, deception and harm while enhancing product safety

**Powers:** Prevent sale/distribution of
- adulterated / mislabelled products
- products manufactured or stored under unsanitary conditions
- misrepresented products

“Drugs”, as defined in the Act, include any substance that is sold to restore, correct or modify organic functions in human beings

“Devices”, as defined in the Act, include any contrivance that is sold to restore, correct, modify a body function or the body structure of human beings

Note – no regenerative medicine products are defined in the Act
Food and Drug Regulations

Policies/guidelines/interpretations

Food & Drug Regs  CTO Regs  Medical Device Regs

Legislative Authority

Basis: Food and Drugs Act
Purpose: delineate prohibited activities from authorised activities
Powers: prohibit distribution of non-compliant manufacturer/importer product, including products that
• represent safety concerns
• lack sufficient evidence regarding their beneficial effect
• are not consistent with interests of research subjects (in clinical trials)

Division 1 - General
Division 1A - Establishment Licensing
Division 2 - Good Manuf. Practices
Division 4 – Biologics
Division 5 - Clinical Trials
Division 8 - New Drugs
Safety of Human Cells, Tissues and Organs for Transplantation Regulations

Basis: Food and Drugs Act

Purpose: establish minimum safety standards for processing activities

Powers: hold “source establishments” accountable for processing activities:
• donor screening, testing, and suitability assessment
• CTO retrieval and preparation for use, except for organs and islet cells
• testing and measurements performed on the cells, tissues or organs after they are retrieved
• Preservation, quarantine, banking, packaging and labelling

Applies to allogeneic applications of CTO that are “minimally manipulated” for “homologous use”, and are not (a) *reliant on their systemic effect / metabolic activity or (b) the subject of clinical investigations
Medical Device Regulations

Legislative Authority

Basis: Food and Drugs Act

Purpose: delineate prohibited activities from authorised activities

Powers: prohibit distribution of non-compliant manufacturer/importer product, including products that
  • represent safety concerns
  • lack sufficient evidence regarding their beneficial effect
  • are not consistent with interests of research subjects (in clinical trials)

Part 1 – General requirements
Part 2 – Custom-made devices, devices to be imported/sold for special access
Part 3 – Medical Devices for Investigational Testing Involving Human Subjects

Schedule 1 – Classification rules for medical devices (risk categories I to IV)
Various policies/guidelines

Policies/guidelines/interpretations

Food & Drug Regs
CTO Regs
Medical Device Regs

Legislative Authority

Food and Drugs Act

Basis: Various

Purpose: to help sponsors understand federal regulatory processes and requirements

Powers: none / indirect
• Intended to be supportive in nature
Management of Drug Submissions in Canada

Purpose: Describes how drug submissions are handled

Scope: All drug submissions

Contents:

• Contact information for Regulatory Affairs Groups
• High level overview of regulatory lifecycle
  • Organising pre-submission meetings
  • Preparing pre-submission packages
  • Requesting priority status
  • How to file a submission / submission timelines
• What happens once a submission is accepted
  • Screening
  • Review
  • Solicited information vs unsolicited
  • “Clarifax” process and expectations
• Possible review decisions and their implications
• Dispute resolution process
Clinical Trial Guidance

Purpose: Describes submission and post-submission procedures and requirements

Scope: All drug Phase I to III & “off label” clinical trials

Contents:
• Pre-Clinical Trial Application expectations
  • Info package structure and contents
  • Post-meeting Records
• CTA content expectations
  • Basic info (indications/populations/route/dose
  • Combination product direction (joint reviews)
  • Submission format (*common tech. document)
  • When & how to do CTA Amendments/Notifications
• Screening, clarifax, and review decision timelines and implications
• Linking REB approval and CTA
• Post-authorization and Safety Reporting req’ts
• Lot release
Clinical Trial Guidance for cell therapy sponsors

Purpose: Describes CTA submission expectations specific to cell therapy products

Scope: Human cell therapy CTAs except for reproduction, gene therapies, or tissue engineered products

Contents:
- Commitment to apply existing regulations, policies and procedures, but consider unique nature of cell therapies
- Cell therapy specific considerations for the following
  - Quality (Chemistry & Manufacturing) requirements
  - Pre-clinical data development
  - Clinical trial design and considerations
  - Clinical trial management and follow-up
Quality (Chemistry & Manufacturing) guidance

- Materials, reagents and excipients should be carefully controlled
  - All product inputs should be tested and assessed against qualifications
  - Evidence of batch control varies according to status of materials (drug/USP/in house”), and needs to be readily available to the regulator upon request
- Human/Animal-Derived Materials require additional screening/testing
  - Methods used to mitigate the risk of transmitting infectious diseases and adventitious agent should be described and compared to existing guidelines
Quality (Chemistry & Manufacturing) guidance

- Processes should be well characterized
  - Critical steps and quality attributes should be identified and carefully supported
  - Appropriate work should be done throughout development to validate processes
  - Special approaches to account for unique nature of cell therapies should be well supported by a rationale and scientific evidence (e.g. working cell bank lot testing)
- The product itself should be well characterized
  - Health Canada puts an emphasis in early phase CTA on Drug Substance and Drug Product specifications that are critical to product safety
  - Evidence to support product specifications, stability and batch-to-batch consistency should be established, justified and tightened throughout pre-clinical and clinical phases of development
Pre-clinical Data Development

• Key safety concerns should be addressed first in animal / *in vitro* studies that should be included and discussed and summarised concisely together in the submission to support the product intended for in humans
  – Toxicity, tumour forming potential, ectopic tissue formation potential, immunogenicity, and biodistribution / engraftment behaviours

• Overall risk estimates should consider tissue source, ability to proliferate / differentiate, immunogenicity, degree of manipulation, mode of adminstration, tumourgenicity, location and duration of engraftment, biodistribution, and potential to transmit infectious diseases
Pre-clinical Data Development

• Preliminary estimates of potential benefits should consider their duration and magnitude of effect and dose / response relationship.
• Other information should be provided to support theories and data to describe mechanism of action and analyses of benefits and limitations of pre-clinical approaches to development.
• Benefits and limitations of *in vitro* bench-top assays, small animal models, and large animal models should be considered, discussed, and supported.
Clinical Data Development

• Early first in human trials using cell therapies should follow general clinical development guidelines for therapeutic products
  – Health Canada recognises that in many cases cell therapies may need to be investigated first in patient sub-populations (not healthy volunteers), and that pre-clinical study data may be limited or of limited use for cell therapy products
• Even early stage clinical trial sponsors should consider long-term safety plans
• Proof of concept studies should consider all pre-clinical evidence and clinical experiences with similar cells to support optimal dose estimation and pharmacodynamic / pharmacokinetic studies
  – Sponsors are encouraged to use extrapolation, modelling, and / or simulation
Clinical Data Development

- Relative clinical effects of excipients and impurities should be considered.
- Clinical efficacy endpoints of pivotal cellular therapy studies may include physiological responses or changes in immune function, gene expression, or cell engraftment.
Clinical Trial Monitoring and Follow-up

• Consideration should be given to identifying subject safety monitoring and clinical trial monitoring
  – Stop rules may be important
  – Interim analyses and repeat dosing may present challenges, and their implications should be discussed with the regulator
• Plans to manage potential risks should be developed
• The utility of long term patient registries should be evaluated at this stage
• Lot release requirements must be followed
  – Details of lot release requirements are determined on a case-by-case basis, and typically require “faxback” information
• Serious unexpected adverse drug reactions must be reported to Health Canada
International Regulatory Perspective

Analogous partners internationally:
• US Food and Drug Administration (US FDA), European Medicines Association (EMA), Japanese Pharmaceutical and Medical Devices Agency (PMDA), etcetera

Harmonization efforts
• Health Canada is now an official member of the International Council on Harmonization (ICH)
  – Refer to Common Technical Documents (CTD)
  – Refer to ICH Guidelines
• Health Canada participates on International Pharmaceutical Regulator’s Forum (Cell & Gene Therapy Groups)

Collaboration efforts
• Health Canada participates in quarterly Advanced Therapy Medicinal Products (ATMP) “Cluster Meetings”
  – EMA/US FDA/Health Canada/PMDA
International guidelines

The CTD Triangle

Module 1
- Regional Admin Information
- Not Part of the CTD

Module 2
- Quality
  - Overall Summary 2.3

Module 3
- Quality
  - Module Study Reports

Module 4
- Nonclinical Overview 2.4
  - Nonclinical Summary 2.6

Module 5
- Clinical Overview 2.5
  - Clinical Summary 2.7
  - Clinical Study Reports

The CTD
International guidelines

US FDA example of ICH CTD format expectations

*Note IND stands for investigational new drug
The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

**Quality Guidelines**
Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

**Efficacy Guidelines**
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

**Safety Guidelines**
ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

**Multidisciplinary Guidelines**
Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRi).
Tips and Tools for Navigating Regulations

• Take advantage of free regulatory interactions at appropriate times
  – Written inquiries
  – Pipeline meetings
  – Pre-Clinical Trial Application
  – Pre-New Drug Submission

• Be prepared to “tell your story”
  – Who are you? Who are you working with? Who are you trying to treat?
  – What is your product? What is your process?
  – Where are you making your product? Where are you getting your materials?
  – How have developed your product? How do you plan to develop it in the future?
  – Why did you select one thing over another? Why should it be authorised?
Tips and Tools for Navigating Regulations

• Ask informed questions that will help you prepare your product submission, and not pre-empt a submission review decision
• Provide all relevant information to support regulatory decision-making
  – Propose a position that is based on Canadian regulation, considers international perspectives & analogous products, and references appropriate Health Canada and ICH guidelines. **Describe and justify deviations**, provide supportive evidence, and expect Health Canada to examine the science carefully from a patient safety perspective
Frequently Asked Questions #1

Why is my product regulated under the *Food and Drug Regulations* vs *Safety of Human Cells Tissues and Organs for Transplantation Regulations* (or vice versa)?

Response:

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Food and Drugs Act

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

Safety of Human Cells, Tissues and Organs for Transplantation Regulations
  - 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

New Drug Submission
Clinical Trial Application
Establishment Registration
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Frequently Asked Questions #2

Will Health Canada develop guidance for gene therapy product sponsors?

Response:

• Preliminary work is being done to communicate environmental assessment requirements for novel viral vectors under the New Substance Notification Regulations
• Pre-submission meetings and US FDA guidance can be used to develop Canadian CTAs
• Health Canada is currently working with international partners to assess regulatory guidance needs for gene therapies
Frequently Asked Questions #3

When do establishments need to be compliant with Good Clinical Practices (GCP), Good Laboratory Practices (GLP), and Good Manufacturing Practices (GMP)?

Response:

• All studies regulated under Division 5 of the *Food and Drug Regulations* must adhere to GCP principles from beginning to end (Consolidated Guidance ICH E6)

• Canadian labs can become GLP accredited by the Standards Council of Canada at any time. All pre-clinical studies should be done in GLP facilities, particularly studies considered “pivotal” for CTAs; however, there is flexibility for Health Canada to consider data from non-GLP accredited facilities, where justified

• Compliance with Division 2 must be demonstrated to BGTD prior to clinical trial authorization or market authorization; however, an establishment is typically not considered “GMP compliant” until it obtains an Establishment License from Health Canada’s Inspectorate for licensable activities
When do establishments need to obtain an Establishment License (EL)?

Response:

• Someone in Canada must obtain an EL if conducting one of the following 6 activities with respect to a “drug”: fabricating, packaging/labelling, importing, testing (for GMP purposes), distributing, and wholesaling
  – EXCEPT if doing so for a clinical trial authorized under Division 5 i.e. you don’t need an EL for a cell therapy product to be used in a clinical trial setting; however, you should begin discussions with Health Canada’s Inspectorate towards later clinical trials to understand how one may obtain an EL before receiving a Notice of Compliance & selling a drug
Frequently Asked Questions #5

How are cell therapies regulated if they are combined with another drug/device or if they modify a body function/structure and have an organic function?

Response:
• Refer to principles found in the Drug/Device Combination Policy and Classification Decisions at the Drug/Device Interface

Classification advice:
• Discuss classification early on to avoid surprises (i.e. ISO vs GMP)
• Make a case referring to legislative definitions using available guidance, but provide all relevant information (even that which does not support your case)
• Consider distribution model affect on implicit claims
Frequently Asked Questions #6

Early authorization opportunities: Will I qualify for Priority Review / a Notice of Compliance with Conditions?

Response:
Only if your product is intended for use in treating serious life threatening diseases/conditions for which there are no other treatments  
AND  
Only once you have accumulated sufficient evidence of clinical safety, and established preliminary efficacy data  
(i.e. typically after Phase II studies or during phase III studies where one cannot complete or wait for phase III studies to conclude)
Frequently Asked Questions #7

Do I need to conduct xyz studies? What are acceptable clinical endpoints/control arms/etc?

Response:
• It depends…

2 Key Messages:
1. totality of evidence must be considered in making regulatory decisions
2. you are best advised that any responses from Health Canada to questions like these are intended to be helpful, but remain dependant upon the available evidence (which may change when all the evidence in a submission package is reviewed)
Contact information

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Thank you

Questions?