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Considerations from the HC perspective for multicentre clinical trials

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Multicentre Clinical Trials

- A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

- A coordinating investigator is assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

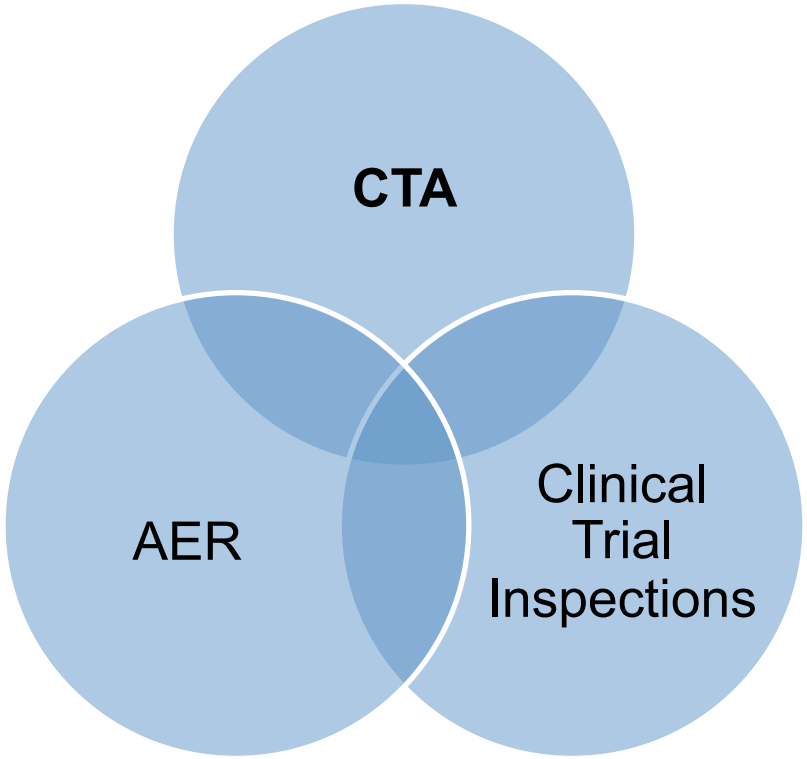
- Carried out for two main reasons:
  - An accepted way of evaluating a new medication more efficiently; under some circumstances, it may present the only practical means of accruing sufficient subjects to satisfy the trial objective within a reasonable time-frame. Multicentre trials of this nature may, in principle, be carried out at any stage of clinical development.

  - To provide a better basis for the subsequent generalisation of its findings. Such a trial is more likely to be a confirmatory trial in the later phases of drug development and would be likely to involve a large number of investigators and centres.

Outline

- Considerations for multicentre Trials
- Cell Therapy Challenges & Regulatory Concerns
- Overview of Clinical Trials Guidance for Cell Therapy Sponsors
- Accelerated Pathways

Clinical Trial Oversight



Division 5 of the *FDR*:

- C.05.001 (Interpretation)
- C.05.002 (Application)
- C.05.003 (Prohibition)
- C.05.005 (Application for Authorization)
- C.05.006 (Authorization)
- C.05.007 (Notification)
- C.05.008 (Amendment)
- C.05.009 (Additional Information and Samples)
- C.05.010 (Sponsor's Obligations – GCP)

Challenges & Regulatory Concerns for Cell Therapies

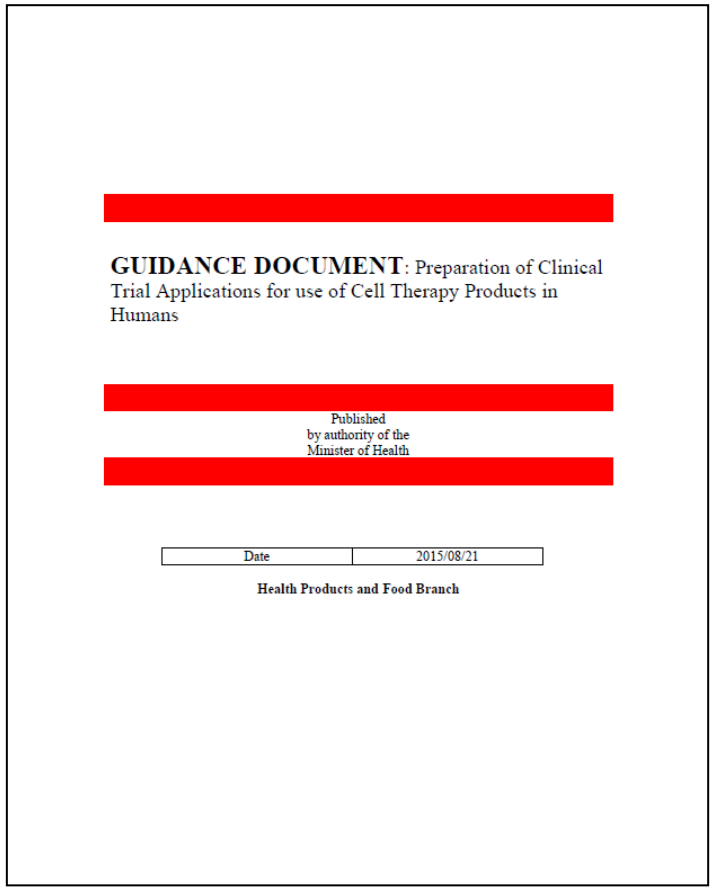
Risk assessment issues:

- 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 & rare indications

Clinical Trial Guidance for cell therapy sponsors



GUIDANCE DOCUMENT: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans

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by authority of the
Minister of Health

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Health Products and Food Branch

Provides information to assist sponsors in interpreting how Part C, Division 5 of the *Food and Drug Regulations* is applied to the authorization of clinical trials using cell therapies

Intended to supplement other HC documents:

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

& adhere to ICH principles such as:

- ICH E2F: Development Safety Update Report (DSUR)
- **ICH E6: Good Clinical Practice (GCP)**
- **ICH E7 - E11: Clinical Trials (General, Special Populations, Statistical)**
- ICH E2E: Pharmacovigilance Planning (RMP)

Also:

- **ICH E17: General principles for planning and design Of multi-regional clinical trials**

Pre-Clinical Studies - Expectations

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

Risk:

- Administration effects
- Tumour formation
- Immunogenicity
- Reproductive effects
- Ectopic tissue formation
- Cardio-pulmonary effects
- Biodistribution and engraftment
- Long-term adverse effects

Benefit:

- Duration of the intended effect
- Reproducibility of the effect
- Mechanism of the effect
- Dose-effect relationships

- **… choice of the experimental model(s) ?**
- **… according to each product inherent risk benefit profile !**

Pre-Clinical Models

Appropriateness of experimental models depend on:

- Anticipated risks associated with product.
  - high risk products require more extensive testing
- Availability of model systems.
  - disease model may yet to be developed
  - multiple models → which one is superior?
- Route of administration.
  - should simulate intended 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 !**

Quality (Chemistry & Manufacturing)

- 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)

- 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)

Quality (Chemistry & Manufacturing)

- 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

Clinical Data Development

- Early first in human trials using cell therapies should follow general clinical development guidelines for therapeutic 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
- Relative clinical effects of excipients and impurities should be considered

Clinical Trial Monitoring and Follow-up

- **Consideration should be given to identifying subject safety monitoring and clinical trial monitoring**
  - Stop rules may be important
- 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

Approval of Cell Therapy Products

Before a new drug is authorized for sale in Canada, the sponsor is responsible for providing the necessary scientific evidence that underpins the benefit-risk assessment in drug regulatory decision making:

- Detailed reports to establish its safety
- Substantial evidence of clinical effectiveness for the intended purpose

Clinical study reports in the literature?

- …are generally considered <u>insufficient</u> to establish the clinical safety and efficacy required under the *Regulations, i.e.* they do not provide substantial evidence of efficacy and safety

Accelerated Pathways

Priority review

- Applies to NDSs and SNDSs for serious, life-threatening or severely debilitating disease for which there is substantial evidence of clinical effectiveness that the drug provides:
  - effective treatment of a disease for which no drug is available; OR
  - Offers a significant increase in efficacy and/or significant decrease in risk over existing therapies for a disease that is currently not adequately managed.

Notice of Compliance with Conditions

- NOC/c clinical eligibility criteria are in line with Priority Review criteria, but applies to products with promising evidence of clinical efficacy

- Health Canada's first cell therapy authorization (Prochymal) relied on NOC/c conditional authorization.

Risk Management Plan for Cell Therapies

Cell Therapy Product considered for market approval **must have a *Risk Management Plan, RMP (Risk Evaluation and Mitigation Strategies, REMS)*.**

The **RMP** document:

- Summarizes all risk information accumulated on the product (safety profile) including that from:
  - -clinical trials
  - -all indications
  - -all dosage forms & strengths
  - -expanded access use (SAP)
  - -off label use
  - -marketed use

- Outlines proposed safety data gathering & monitoring activities
- Describes risk minimization strategies

Sponsors should begin the **planning and development** of the RMP during **early** clinical phases of product development.

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?

Contact information

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