





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



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Health Products and Food Branch

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Health Canada – Publications
Brooke Claxton Building, A.L. #0913A
Tunney's Pasture
Ottawa, Ontario
K1A 0K9

Tel: (613) 954-5995
Fax: (613) 941-5366

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FOREWORD

Guidance documents are meant to provide assistance to industry and health care professionals on **how** to comply with governing statutes and regulations. Guidance documents also provide assistance to staff on how Health Canada mandates and objectives should be implemented in a manner that is fair, consistent and effective.

Guidance documents are administrative instruments not having force of law and, as such, allow for flexibility in approach. Alternate approaches to the principles and practices described in this document ***may be*** acceptable provided they are supported by adequate justification. Alternate approaches should be discussed in advance with the relevant program area to avoid the possible finding that applicable statutory or regulatory requirements have not been met.

As a corollary to the above, it is equally important to note that Health Canada reserves the right to request information or material, or define conditions not specifically described in this document, in order to allow the Department to adequately assess the safety, efficacy or quality of a therapeutic product. Health Canada is committed to ensuring that such requests are justifiable and that decisions are clearly documented.

This document should be read in conjunction with the accompanying notice and the relevant sections of other applicable guidance documents.

Note:

In this document, "sponsor" refers to stakeholders that have submitted an application to Health Canada for approval to distribute a drug in Canada for the purposes of clinical investigation.

In this document, "shall" is used to express a requirement, i.e., a provision that the user is obliged to satisfy in order to comply with the regulatory requirements; "should" is used to express a recommendation which is advised but not required; and "may" and "can" are used to express an option which is permissible within the limits of the guidance document.

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1. INTRODUCTION

1.1 PURPOSE

The purpose of this guidance is to provide information to prospective cell therapy product clinical trial sponsors to assist them in satisfying applicable Federal regulatory requirements as set out in *Division 5 – Clinical Trial Applications* of the *Food and Drug Regulations*.

1.2 SCOPE AND APPLICATION

For the purposes of this document, "cell therapy products" includes human cells of somatic (fetal, neonatal and adult) or embryonic origin that are used for investigative purposes. This includes both cells derived from the individual undergoing treatment (autologous) as well as from donated tissues (allogeneic) and encompasses induced pluripotent stem cells or other cells in which the differentiation potential has been altered or enhanced.

This document applies to cell therapy products at the investigational stage and takes into consideration some of the unique characteristics of cell therapy products. It supports the risk/benefit analysis framework that is the cornerstone of Health Canada's review process and addresses cell therapy products that meet any of the following criteria:

- cell therapy products that have a systemic effect and depend on their metabolic activity for their primary function
- cell therapy products whose local effect and type of activity has not yet been established
- cell therapy products that are considered "more than minimally manipulated"
- cell therapy products for "non-homologous use"

The Department will take a precautionary approach in deciding if a cell therapy is minimally manipulated and for homologous use to fall under the *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (CTO Regulations). It will look to stakeholders to provide clear evidence establishing these criteria are met before deciding a cell therapy is governed by the CTO Regulations.

This document should be used in conjunction with existing Health Canada guidance to sponsors of Clinical Trial Applications (CTAs).

Exclusions

This guidance does not apply to gene therapy products, including cells that have been genetically manipulated such that the therapeutic function of the product is afforded by the introduced gene(s).

In addition, this guidance does not apply to cells and tissues used for human assisted reproduction purposes.

1.3 POLICY STATEMENTS

The following statements outline the fundamental concepts and principles used for the regulation of cell therapy products at the investigational stage in Canada:

- 1.3.1 The sponsor is responsible for providing the necessary evidence to support all aspects of an application for authorization.
- 1.3.2 Regulatory decisions regarding cell therapy products will be based on the *Food and Drugs Act* and *Regulations*. The concepts and scientific and regulatory principles within the existing regulatory frameworks and policy documents for biologic drugs are used as the basis for regulating cell therapy products.
- 1.3.3 Basic donor screening and testing requirements under the CTO Regulations provide a good basis for determining appropriate screening and testing for cell therapy products, although the CTO Regulations do not apply to these products. Any relaxation of the currently accepted donor screening or testing practices should be supported by evidence and/or rationales.
- 1.3.4 Classification decisions and regulatory pathways for drug-device combination products involving a cell therapy product component can be determined based on principles described in Health Canada's *Drug/Medical Device Combination Products Policy*.

1.4 BACKGROUND

Cell therapy products encompass a diverse range of products including, but not limited to stem cells of embryonic, fetal, induced pluripotent or adult origins, and cells at various stages of differentiation. These products can differ greatly in their biological function, tissue of origin, self-renewal capacity, migratory ability, paracrine function, tissue engrafting potential and potential to proliferate, differentiate and form tumours. Equally diverse is their therapeutic utility toward tissue restoration and replacement, immune system modulation and treatment of congenital diseases. As such, each cell therapy product is associated with a unique risk/benefit profile. Accurate risk/benefit assessment and communication is a necessary step in the development and then utilization of cell therapy products.

Risk/benefit analyses should be supported by reliable scientific data obtained from well controlled and properly planned pre-clinical and clinical studies. The development of such studies requires in-depth background knowledge and understanding of the potential risk of harm and intended benefit associated with the product itself.

When assessing the potential risks associated with cell therapy products, both cell inherent risks and risks that are introduced during processing and manufacturing, must be taken into account. Many risks associated with cell therapy products can be mitigated through tightly controlled manufacturing processes. Other risks can be identified and avoided with information from adequately designed pre-clinical and clinical investigations. Residual risks can be communicated to physicians and potential recipients so that they may make informed decisions.

1.5 TERMINOLOGY

Acronyms and Abbreviations

BGTD = Biologics and Genetic Therapies Directorate
CTA = Clinical Trial Application
CTA-A = Clinical Trial Application Amendment
CTD = Common Technical Document
CTO = Cells, Tissues and Organs
CTO Regulations = *Safety of Human Cells, Tissues and Organs for Transplantation Regulations*
DIN = Drug Identification Number
DP = Drug Product
DS = Drug Substance
GCP = Good Clinical Practices
GLP = Good Laboratory Practices
GMP = Good Manufacturing Practices
ICH = International Conference on Harmonisation
MCB = Master Cell Bank
TSE = Transmissible Spongiform Encephalopathies
USP = United States Pharmacopoeia
WCB = Working Cell Bank

Definitions

- **Adventitious agents:** Microbiological contaminants that may be inadvertently introduced during the manufacturing process of a biologic drug.
- **Allogeneic use:** Transplantation of cells or tissues from one individual to another. Also known as an allograft.
- **Autologous use:** Transplantation of cells or tissues removed, processed and returned to the same patient. Also known as an autograft.
- **Ancillary materials/reagents:** Any reagent used in drug manufacturing that is not intended to be present in the final product.
- **Biologic drug:** Drugs listed in Schedule D to the *Food and Drugs Act*.
- **Biological starting material:** Material from a biological source which is intended to be used in the manufacture of a substance from which the active ingredient is derived either directly (e.g., bone marrow, blood, tissue, etc.) or indirectly (e.g., cell substrates, host/vector production cells, eggs, viral strains etc.).

- **Drug product (DP):** The final dosage form of a drug that is placed in the immediate packaging intended for marketing.
- **Drug substance (DS):** A defined process intermediate containing the active ingredient, which is subsequently formulated with excipients to produce the drug product.
- **Establishment:** Any enterprise, utility or body that is involved in any aspect of the processing, manufacturing, storage and/or distribution of a drug.
- **Good Laboratory Practices (GLP):** The organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded, archived and reported.
- **Good Manufacturing Practices (GMP):** A defined system of determinants and controls for quality production, applicable to the manufacturing of drugs (see Division 2 of the *Food and Drug Regulations*). Division 1A, Part C of the *Food and Drug Regulations* defines activities for which GMP compliance is to be demonstrated prior to the issuance of a drug establishment licence.
- **Homologous Use:** In respect of a cell, tissue or organ, the cell, tissue or organ performs the same basic function after transplantation.
- **Immunogenicity:** The ability of a product to induce an immune response, which can be influenced by various factors, including patient-/disease-related factors and product-related factors. This response is complex and can include antibody formation as well as other events such as T cell activation or innate immune response activation that could contribute to adverse responses.
- **Impurity:** Any component of the drug product that is not the drug substance or an excipient in the drug product.
- **Minimally Manipulated:** In respect of cells and non-structural tissue, that the processing does not alter the biological characteristics that are relevant to their claimed utility (for examples, see Section 2 of the *Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation*).
- **Quality Assurance (QA):** All planned and systematic activities implemented within the quality system and demonstrated as needed to provide adequate confidence that an entity will fulfil requirements for quality.
- **Quality Control (QC):** Operational techniques and activities that are used to fulfil requirements for quality in compliance with the specification.
- **Raw Material:** Any materials used in manufacturing that are procured from outside sources.
- **Somatic cells:** Any cells that have differentiated (i.e., not stem cells or gametes).
- **Specification:** A predefined combination of testing methods and acceptance criteria intended for routine quality control of materials for and from manufacturing including but not limited to raw materials, starting materials, drug substance, drug product and packaging materials.
- **Starting Materials:** Materials which are intended to be used in the manufacture of a drug substance and from which the active ingredient is derived either directly or indirectly.

- **Transmissible Spongiform Encephalopathies (TSE):** All progressive neurodegenerative disorders caused by prions in animals and humans that produce spongiform changes in the brain.

2. GUIDANCE FOR IMPLEMENTATION

2.1 APPLICABLE REGULATIONS

The *Food and Drugs Act* provides legislative authority to Health Canada to regulate the sale of drugs for use in human clinical trials in Canada. Cell therapy products are considered “drugs” as defined under this Act; Health Canada’s Biologics and Genetic Therapies Directorate (BGTD) regulates cell therapy products under Part C, Divisions 1, 1A, 2, 4, 5 and 8 of the *Food and Drug Regulations*.

Of particular note for the purposes of this guidance is **Part C, Division 5** of these regulations, which pertains specifically to drugs for clinical trials involving human subjects. Division 5 stipulates what criteria must be met and what information shall be submitted to Health Canada in a CTA to support an application for authorization of the trial in Canada. Division 5 also stipulates the information that shall be submitted in a Clinical Trial Application Amendment (CTA-A) in the event of a change that meets any criteria listed in C.05.008(2) (a) to (f).

Pursuant to C.05.006 of the *Food and Drug Regulations*, clinical trial sponsors may commence the clinical trial, or initiate an amendment, either upon receiving a No Objection Letter from Health Canada or 30 days following the date of receipt of the application by Health Canada.

2.2 GENERAL GUIDANCE

Regulatory decisions regarding CTAs are made by Health Canada on a case-by-case basis following an assessment of the scientific information provided by submission sponsors. Health Canada may also take into consideration scientific information and data that is publicly available; policy principles outlined in Health Canada guidance documents; and/or international policies that pertain to cell therapies as deemed appropriate by Health Canada. To support regulatory decisions, Health Canada may require a CTA sponsor to submit, within two days after receipt of the request, additional information relevant to the drug or the clinical trial that are necessary to make the determination of safety.

2.2.1 Considerations for cell therapies at different stages of development

Health Canada recognizes that cell therapy products have a life-cycle that starts from basic research where relatively little can be known about their benefits and risks and progresses through early stage clinical trials, then later stage clinical trials, where increasingly more is known about their benefits and risks, until enough is known to support market authorization. Sufficient regulatory flexibility in the *Food and Drug Regulations* exists to allow research to move forward. Throughout cell therapy product development stages, the amount of product characterization and manufacturing, pre-

clinical and clinical information required to support the authorization of a clinical trial will be directly related to a case-by-case risk assessment that considers the developmental stage of the product.

While a typical approach to drug development is step-wise in nature, the traditional clinical approach of progression through Phase I, II and III investigations may not be applicable to certain cell therapy products. As such, the clinical investigative stages of a cell therapy product will be grouped into “early” and “late” phase clinical trials for the purposes of this guidance. Early trials will include first in human trials and dose determination / tolerance studies with primary endpoints focussed on product safety. Early trials may also be conducted to provide proof of concept. Such trials should be designed to sufficiently support the initiation of late phase trials and pivotal trials that investigate product efficacy in larger patient populations.

Health Canada encourages sponsors to engage in pre-submission meetings, whether in person or via teleconference, prior to the preparation and submission of a CTA. Such meetings provide an opportunity to discuss details of the submission and obtain direction for potential areas of concern and the information that is required to support clinical trial applications for authorization. Requests for information via email from the sponsor to Health Canada can also be made to support cell therapy CTA submissions.

2.2.2 Additional references

Clinical Trial sponsors should consult the Health Canada Guidance Document *Guidance for Clinical Trial Sponsors - Clinical Trial Applications*, which outlines the general regulatory requirements for clinical trials and provides contact information for engaging in pre-submission meetings.

To supplement information from this guidance document, cell therapy CTA sponsors should follow principles, definitions and standards documented in International Conference on Harmonization (ICH) guidance. As a Steering Committee member to the International Conference on Harmonization (ICH), Health Canada is committed to the adoption and implementation of ICH guidance documents. A list of relevant ICH safety, efficacy and quality guidance documents is included in the appendix C.

2.3 MANUFACTURING AND QUALITY ASSURANCE GUIDANCE

Section C.05.010(f) of the *Food and Drug Regulations* require drugs for clinical trials to be manufactured, handled and stored in accordance with the applicable Good Manufacturing Practices (GMP) referred to in Division 2 (except specific sample testing and retention requirements described in C.02.019, C.02.025 and C.02.026). Sponsors are referred to GUI-0036 for general guidance for drugs used in clinical trials. Cell therapies will be held to increasingly stringent manufacturing controls as they are developed from early to late stage clinical trials.

The development of a cell therapy product can involve novel, unique and complex manufacturing processes that may be associated with long-term safety concerns. This

section will discuss some of the challenges associated with cell therapy product manufacturing and provide recommendations regarding the type of chemistry and manufacturing information that should be submitted in a CTA to Health Canada.

A cell therapy product, as for any drug intended for clinical use, should be produced via an adequately characterized robust manufacturing process governed by quality assurance and quality control measures sufficient to ensure production of a consistent and reproducible product. It is recommended that discussions regarding the manufacturing process be initiated with Health Canada prior to the filing of any CTA (e.g. within the context of a pre-submission meeting). To enable discussion and the provision of advice, sponsors should submit a concise summary of the manufacturing process with emphasis on the critical manufacturing issues addressed in this guidance.

When submitting a CTA to Health Canada, all quality information should be provided in the Common Technical Document (CTD) format and template as suggested by the ICH. Specific references to CTD modules are made below, which can be used in conjunction with ICH guidance documents that have been adopted by Health Canada.

It may not be necessary to complete all elements of the CTD document during early stages of clinical development. Instead, information obtained during early phase studies can be incorporated into the document for later stages of product development such that all components are in place prior to the administration of product to larger patient populations.

Manufacturing changes to cell therapy products being investigated in Canada must be reported to Health Canada in one of two ways, depending on whether the change affects the safety of the cell therapy being investigated: (1) A CTA sponsor must submit a CTA-Amendment to Health Canada for review before implementing a manufacturing change that could affect the safety of the cell therapy. For example, a change to donor screening and testing requirements would require a CTA-Amendment. (2) A CTA sponsor must notify Health Canada in writing about manufacturing changes that do not affect the safety. For example, tighter quality control specifications made from experience in manufacturing of the product would not require a CTA-Amendment, and can be implemented after providing Health Canada with written notification.

2.3.1 Control of materials, reagents and excipients

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials*

Materials, reagents and excipients must be tested and assessed against pre-determined or otherwise written specifications. The testing and assessment of materials before use has the following objectives:

- to confirm the identity of the materials;
- to assure that the materials have the characteristics that will provide the desired quantity or yield in a given manufacturing process;

- to provide assurance that the quality of the drug in dosage form will not be altered by variability in the materials; and
- to ensure they are safe for the intended use.

This section pertains to all manufacturing materials (including starting materials, raw materials, and ancillary materials), reagents, and excipients. Additional considerations including screening and testing requirements for human and animal derived materials, reagents, and excipients are discussed in Section 2.3.2 of this guidance.

All manufacturing materials, reagents, and excipients must be adequately controlled by CTA sponsors to mitigate cell processing risks. In addition to being important to the safety of clinical trial subjects, well controlled cell product manufacturing throughout product development can best support later clinical trials applications and eventual market authorization requests. Ideally, manufacturing materials, reagents, and excipients will be consistently controlled throughout all stages of development, or meet increasingly stringent controls throughout all stages of development. Any changes to material, reagent or excipient controls that represent loosening of criteria will require a strong rationale and additional information and evidence to support changes.

In early stages of clinical product development, qualification of manufacturing materials, reagents, and excipients should be focussed on safety. As development progresses and the manufacturing processes become better defined, qualification programs should support the development of a consistent and effective product.

2.3.1.1 Types of evidence to support control of materials in a cell therapy CTA

When drugs are used as manufacturing materials, reagents, or excipients to fabricate a cell therapy product, a valid Canadian Drug Identification Number can provide Health Canada sufficient indication of safety and quality for use by a clinical trial sponsor. Alternatively, if the drug is not authorised for sale in Canada, sufficient information must be submitted by the CTA sponsor to enable Health Canada to assess its quality and the associated risk of its proposed use in the clinical trial.

For GMP or pharmacopeial grade manufacturing materials, reagents, and excipients that are sourced externally and are not approved drugs in Canada, CTAs may be supported by evidence of adequate quality control in the form of an up to date Certificate of Analysis (CoA). While the CTA sponsor will need to (a) review CoA for each lot prior to its use to fabricate cell therapies and (b) have a system in place to periodically confirm testing, Health Canada does not review a CoA for every batch used, and a representative batch analysis may be considered acceptable where a rationale supporting the sampling is provided.

For manufacturing materials, reagents, and excipients that are not authorised drugs, GMP grade, or pharmacopeial grade, or where evidence of GMP/pharmacopeial grade is not provided, manufacturers must provide Health Canada with evidence that appropriate

controls are in place and functioning to assess and mitigate the level of risk associated with their use.

In the case where drugs are used as excipients, suitable evidence should be accumulated to demonstrate that any clinical effects are not due solely to the excipient itself.

In cases where CTA sponsor's access to information about materials, reagents and excipients is limited (e.g., for proprietary reasons), and necessary evidence of GMP cannot be made available in the sponsor's CTA, Health Canada can be provided with access to this information in the form of a Drug Master File.

2.3.2 Additional considerations for the Control of Human/Animal-Derived Materials

Recommendation – Include information in

- *CTD Module 3.2.S.2.3. Control of Materials (with appropriate cross-referencing to CTD Module 3.2.S.2.2 – Description of Manufacturing Process and Process Controls)*

In many cases, starting material for cell therapy products will be primary (freshly isolated) cells, tissues or organs of human origin, but may also include previously established lines of human cells. While there are inherent safety risks associated with the use of such materials, these risks can be appropriately mitigated through meticulous controls including screening and testing. In particular, infectious diseases and TSE risks are addressed below.

In addition, since cell therapy products manufactured using human or animal derived reagents or excipients can be considered higher risk, a sufficient rationale should be provided for their use.

2.3.2.1 Infectious Disease Screening and Testing Procedures

While manufacturing steps may be employed to selectively inactivate and reduce pathogens in donated human material, there is no opportunity to sterilise products containing living cells. As such, the potential for transmission of infectious diseases through cell therapy products must be carefully addressed, and this risk should be mitigated through appropriate controls including an acceptable combination of **donor screening** and **donor testing**.

- Donor screening involves the completion of a medical and social history questionnaire and a physical examination. It is important to inform donors of the infectious disease risks associated with the therapeutic use of the products derived from their donations to ensure they are aware of the importance of responding accurately to the questionnaire.
- Donor testing involves the use of devices or equipment to detect relevant infectious disease agents or diseases.

While the CTO Regulations do not apply directly to cell therapy product sponsors, these regulations (along with associated Standards and Guidance) provide a good reference point for what infectious disease screening and testing procedures are expected by Health Canada in order to meet the general obligations of the *Food and Drugs Act*; therefore, cell therapy product sponsors should identify and justify any deviations from these screening and testing requirements in a CTA.

It remains the responsibility of manufacturers to adequately address risks of transmitting infectious disease via their cell therapy products. A 3rd party may be used to screen, test, and collect from human cell or tissue donors. 3rd party testing laboratories and cell or tissue banks should be licensed in their respective jurisdictions, wherever required/possible.

In the case where a 3rd party establishment (such as a cord blood bank or established stem cell line distributor) provides cell therapy manufacturing material that was stored before the cell therapy product was conceived, the cell therapy CTA sponsor will need to demonstrate how the 3rd party screening, testing and record-keeping adequately addresses the risk of transmitting infectious diseases from donors. It is possible that inadequate screening, testing or record-keeping practices may require donor re-screening and/or re-testing. This will depend in part on a benefit-risk assessment that specifically looks at residual risk and how effective these methods would be in reducing residual risks.

Regardless of the regulatory status of 3rd party establishments, the cell therapy CTA sponsor should have reasonable linkages, agreements, record-keeping, information sharing, and change management in place. A responsible cell therapy product manufacturer will also plan to perform periodic audits to confirm that appropriate screening and testing is being done on its behalf. In the case that an establishment is registered by Health Canada, this can be used as supportive evidence that donor material was appropriately screened and tested.

2.3.2.2 TSE Risk

In the absence of a suitable test for prion contamination, manufacturers of cell therapy products are required to anticipate the potential for TSE risks. Quality control programs should appropriately manage these risks and account for any changes that may occur in the TSE risk profile of the product. The level of risk associated with the use of animal derived materials in cell therapy manufacturing is dependent upon several issues. These include, but are not limited to, the country of origin of the material, the TSE risk reduction measures employed by the country, the TSE tissue infectivity, and whether the material is an ancillary reagent or excipient.

Specific Health Canada recommendations for managing BSE/TSE risks are described in the Guidance Document *'Regulatory Requirements to Minimize the Risk of Transmission of Transmissible Spongiform Encephalopathies (TSEs) via Animal-Sourced Materials*

used in the Manufacture of Schedule D (Biologic) Drugs, which is available upon request by sending an email to bgtd.opic@hc-sc.gc.ca.

2.3.3 Process Characterization

Recommendation – Include information in

- CTD Module 3.2.S.2.2. Description of Manufacturing Process and Process Controls
- CTD Module 3.2.S.2.3. Control of Materials
- CTD Module 3.2.S.2.4. Controls of Critical Steps and Intermediates
- CTD Module 3.2.S.2.5. Process Validation and/or Evaluation
- CTD Module 3.2.S.2.6. Manufacturing Process Development

2.3.3.1 Critical Steps and Intermediates

Manufacturers are advised to consider the quality attributes, quality parameters and process controls that are critical to the development of a safe and effective cell therapy product. It is important that each of these steps is identified as well as any parameters that must be met for the manufacturing process to be successful. It is recommended that specifications be put in place to measure important parameters at each of the critical steps identified. These could be specifications that monitor equipment used during the step or that measure the quality of intermediates formed. While ICH Q11 does not apply to contents of submissions during the clinical research stages of drug development, the principles therein may be important for cell therapy sponsors to consider during investigational stages.

2.3.3.2 Process Validation

In early clinical stages only minimal process validation is required for cell therapy products, with a major focus on aspects that are critical to safety. This would include validation and/or evaluation studies for aseptic processing and equipment sterilization and evidence that validated assays are used for measurement of safety parameters, such as sterility, endotoxin, and mycoplasma.

Additional process validation measures should be included as development of the cell therapy product progresses to late clinical phases. Any process change(s) made throughout the developmental stages of the product should be described and rationalized. The significance of any process change should be assessed by evaluating its potential to impact product quality. Comparability studies are the preferred method for completion of such assessments. In later stage investigational studies, sufficient validation data should be accumulated to demonstrate that the manufacturing process is robust and consistent.

For many cell therapy products, each new product lot will be derived from a separate tissue donor. As a consequence, a high degree of lot to lot variation may be associated with cell therapy products compared to traditional biologics and pharmaceuticals. Such process variation can make validation inherently difficult, and yet particularly important. This will especially be the case for directed allogeneic or autologous derived products

where lots are comprised of a single dose derived from a single donor for a specific patient. A well-controlled and validated process can help to reduce lot to lot variation by reducing potential variability associated with the manufacturing process itself.

The time sensitive nature or limited sample availability for some cell therapy products may prevent complete and thorough testing prior to administration. In such cases, a well characterized and validated manufacturing process will reduce the chances of administering a product that does not meet appropriate safety and potency specifications.

2.3.3.3 Cell Banking Systems

In some cases, manufacturing for cell therapy products will involve the creation of Master Cell Bank (MCB) and Working Cell Bank (WCB) intermediates. Specifications should be developed to allow a measure of quality for all cell banks. These specifications should be sufficient to address the suitability of the banked cells for use in subsequent manufacturing stages. For traditional biologics, specifications must be measured for each lot within the MCB and WCB. Health Canada acknowledges that it may not be possible to test each WCB lot for all cell therapy products. In such cases, and with proper justification, statistical approaches may be used to analyze the variability among random lots within each bank.

Measuring the stability of MCBs and WCBs over the proposed period of storage is also critical. More details on measuring product stability are provided in subsequent sections of this document.

2.3.4 Product Characterization

Recommendation – Include information in

- *CTD Module 3.2.S.3. Characterization (drug substance)*
- *CTD Module 3.2.S.3.2. Impurities (drug substance)*
- *CTD Module 3.2.S.4. Control of Drug Substance*
- *CTD Module 3.2.S.4.1. Specification (drug substance)*
- *CTD Module 3.2.S.4.4. Batch Analyses*
- *CTD Module 3.2.S.4.5. Justification of Specifications (drug substance)*
- *CTD Module 3.2.P.4.1. Specifications (drug product)*
- *CTD Module 3.2.P.5.6. Justification of Specification(s) (drug product)*

2.3.4.1 Drug Substance / Drug Product Identification

While differences do exist regarding manufacturing concerns for cell therapy products and other biologic drugs, Health Canada maintains common definitions for Drug Substance (DS) and Drug Product (DP) for all health products regulated in Canada.

The DS contains the active ingredient that is intended to furnish pharmacological activity. Generally speaking, Health Canada considers the manufacturing output just prior to the

final formulation as the DS. The final formulated product in the presentation that is intended for patient administration is considered the DP. These designations are set to provide appropriate time points for monitoring the product manufacturing process and assessing product quality, prior to product release and administration to patients.

Health Canada acknowledges that, for some cell therapy products the DS and DP manufacturing occurs in a continuous process. In these cases, identification of a distinct or separate DS and DP as required in the Drug Submission Template in CTD format may be challenging. The CTA sponsor should identify a DS at a reasonable point in time as close to the Drug Product formulation that allows appropriate testing and characterisation. The choice of DS should be supportable (i.e., it allows appropriate characterisation important to DP preparation).

The DS section of the CTD module will contain information regarding manufacturing that occurs up to that point in the overall manufacturing process, and this information does not need to be re-submitted under the DP section. The DP section of the CTD module will contain information on manufacturing that occurs to prepare the DP from the DS.

2.3.4.2 *Specifications*

DS and DP specifications are an important tool for establishing and monitoring the quality of the manufacturing process and setting limits for key parameters of a cell therapy product. Specifications should monitor key aspects of product quality, taking into account both the safety and potency. Examples include, but are not limited to, cell viability, cell identity, cell yield/number/concentration, cell composition, purity, potency and contamination from adventitious agents, bacteria, endotoxin or mycoplasma. Health Canada acknowledges that in cases where the DS and DP manufacturing is a continuous process, it may not be feasible to test all parameters for the DS. Furthermore, in cases where the DP has a relatively short shelf life and must be released prior to obtaining all test results (e.g., sterility), the lot release specifications may not include tests for all relevant parameters. In these cases, the missing tests should be performed as in process controls and as close to the DP as possible.

It is understood that the development of specifications based on pre-clinical data may be difficult in the early stages of drug development. Therefore, Health Canada puts an emphasis on specifications critical to product safety during the early clinical phases of the product life cycle. It is expected that product specifications are established, justified, and tightened throughout pre-clinical and clinical phases of development of a cell therapy product, incorporating the knowledge generated from accumulated safety and efficacy data. Towards later-phase clinical investigations, final product specifications should be in place to allow sufficient and accurate evaluation of quality that is linked to the clinical outcome of a cell therapy product. It is recommended that these specifications include a measurement of product potency.

2.3.4.3 Batch Analysis

Finished product tests complement the controls employed during the manufacturing process. It is the responsibility of each manufacturer to implement the test methods and set adequate specifications that will help ensure that each cell therapy product is consistently safe for administration.

The results of several product batch analyses should be evaluated as a measure of process variability. Where practicable, batch analysis should be completed on both the DS and DP to fully assess product consistency. This data should be accumulated throughout clinical development of the product so that there is ample data to support process consistency once the product moves out of clinical development phases. Batch analysis testing should assess all DS and DP specifications and the presence or absence of potential impurities whenever possible.

Batch-to-batch consistency, with results within established acceptance criteria, should be demonstrated with three consecutively/ manufactured batches of DP. In cases where one batch of starting material can be used to produce different batches of DP, data should be provided for the three batches of DP manufactured using three consecutive starting materials or any other acceptable process validation approach. Other approaches may be considered appropriate if supported by a strong rationale and / or evidence. Ultimately, the validation approach chosen should account for the potential variability in both the starting material and the DS.

Submission of batch analysis data is also recommended for autologous and directed allogeneic products whenever possible. In cases where the amount of product generated prohibits the completion of batch analysis, or where it is not feasible to manufacture these products before the clinical trial, the manufacturing and analysis of test batches derived from healthy donors may provide a suitable alternative. When completing test batch studies, sponsors should be aware of any potential differences between healthy individuals and patients who may enrol in the study and how the manufacturing process may be affected by such differences.

2.3.4.4 Characterization of Impurities

The complexity of biological products highly impacts the case-by-case evaluation of process- and product-related impurities, and those which may be considered acceptable at each stage of product development.

Cell therapy products may contain several types of impurities, for example;

- non-viable cells
- cell types that do not contribute to the mechanism of action for the cell therapy
- cells with unwanted growth potential
- cell substrate-derived impurities (*e.g.*, host-cell proteins and DNA)
- adventitious agents
- particulate material

- agents added during processing/manufacturing (DMSO etc.)

Such impurities may be associated with safety concerns, such as toxicity; tumourigenicity; immunogenicity; and residual activity.

In all cases, the chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities [see ICH Q2(R1)].

2.3.4.5 Adventitious Agents

Manufacturing processes for cell therapy products are particularly vulnerable to the introduction of adventitious agents since many approaches to inactivation or clearance are not appropriate for a live-cell-based product. A strategy for identifying and addressing the risk of adventitious agents must be clearly identified in a CTA. This strategy should consider the appropriateness of addressing adventitious agents through raw material testing, in-process testing, and final product testing.

Tissue handling, cell manipulation at biological temperatures and the use of animal sourced materials are examples of manufacturing steps that may require specific control measures to reduce the risk of adventitious agent contamination. Each manufacturing step should be well characterized and stages that are associated with a high risk of introducing adventitious agents should be identified. An integrated sterility assurance system should be used to avoid introducing adventitious agents during a given manufacturing step. This could include the use of closed system manufacturing or an advanced manufacturing system. Sterility testing should be intermittently completed on intermediates arising from high risk steps to monitor potential introduction of adventitious agents.

Raw materials of human or animal origin are a potential source of contamination by adventitious agents. Information supporting the absence of adventitious agents in materials of human or animal origin should be provided. This information should include bacterial and fungal sterility and endotoxin testing as well as viral safety data for common viruses associated with the species of origin. Where tests are not done on raw materials and a sample of raw material is not kept for a given batch, it will be difficult to determine whether adventitious agents were introduced through raw materials or through the cell therapy processing itself – for example, where final product mycoplasma tests are positive the cell therapy, CTA sponsor may have difficulty in identifying the step at risk and supporting proposed risk management strategies.

It is important that at least one sample from each DP lot is tested for the presence of adventitious agents. For directed allogeneic or autologous products, an analysis of each DP lot is often not feasible. In these cases process controls are critical for managing and mitigating the risk of introducing adventitious agents.

Mitigation of risk to patients from adventitious agents should be outlined and explicitly addressed in a Risk Management Plan. This should include a description of what

activities will occur when adventitious agents are detected via test results available only after cell therapies have been administered.

2.3.4.6 Stability Testing

Recommendation – Include information in

- CTD Module 3.2.S.7. Stability

The *Food and Drug Regulations* require that each manufacturer establish the period of time that DS or DP will maintain compliance with the finished product release specifications. This is generally determined by implementation of a stability studies program.

Even for the purposes of early clinical trials, manufactures are expected to provide information on the maintenance of critical safety parameters and, where possible, potency (number, identity, viability, etc.) of cell therapy products directly following manufacturing, following storage and/or transportation, and directly prior to administration. The product shelf-life following manufacturing may be determined using stability studies that test a range of storage times and conditions and encompasses all expected extremes when practicable.

Stability studies should be reassessed throughout the product life-cycle to encompass any changes in the manufacturing or storage and transportation processes. Stability studies should be revisited in accordance with changes to release specifications; however, Health Canada recognizes that some testing may be difficult due to product lot size constraints. The feasibility of complete specification testing during stability studies will be considered on a case by case basis and sponsors should provide sufficient rationale to support any proposal for reduced testing.

2.4 PRE-CLINICAL AND CLINICAL GUIDANCE

2.4.1 General criteria for estimating risk in a clinical context

Part C, *Division 5 – Clinical Trial Applications* of the *Food and Drug Regulations* defines Good Clinical Practices (GCP) as generally accepted practices that are designed to ensure the protection of the rights, safety and well-being of clinical trial subjects and other persons. In particular, sponsor's GCP obligations are listed under C.05.010, and are expanded upon in ICH E6(R2).

A CTA may be refused if it runs contrary to GCP, and in particular if (A) the risk benefit ratio of the cell therapy is not acceptable; (B) the clinical trial is contrary to the best interests of the subject; or (C) the objectives of the clinical trial will not be achieved. For cell therapy products, the following general criteria (non-exhaustive) can be used to estimate an overall level of risk that may be associated with its use:

- Donor sourced tissue of origin (autologous/allogeneic; embryonic/fetal/adult; blood/ liver/ neuronal)
- Ability to proliferate and/or differentiate;

- Ability to initiate an unintended immune response (immune rejection and persistence);
- Level of cell manipulation (*in vitro/ex vivo* expansion/activation/ differentiation /genetic manipulation/ cryo-conservation);
- Mode of administration (e.g., *ex vivo* perfusion, injection, local or systemic surgery);
- Tumour forming potential;
- Risk of viral transmission;
- Location and duration of engraftment;
- Biodistribution;
- Combination product (cells and bioactive molecules or structural materials);
- Availability of pre-clinical or clinical data on similar products.

2.4.2 Pre-Clinical Studies

Pre-clinical studies are required prior to the initiation of any investigations for use of a cell therapy product in humans. These may be conducted *in vitro* or in animal models to address the potential risks associated with both the product and its method of delivery. Health Canada will consider findings from pre-clinical studies in Canada or abroad based on their scientific merit. In addition, pre-clinical studies can establish scientific rationale to support clinical utility. General principles on pre-clinical safety studies can be found in *ICH Topic S6 (R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*. Studies and endpoints commonly considered relevant to pharmaceutical and biological drugs may not be relevant when evaluating preclinical safety of cell therapy products. Choice of model system, study type and endpoints should be based on careful consideration of relevance to humans with a case-by-case approach.

2.4.2.1 The importance of Good Laboratory Practices (GLPs)

Pre-clinical studies that are considered pivotal for risk evaluations should adhere to Good Laboratory Practices (GLP). However, supportive pre-clinical studies do not always have to be GLP compliant. The need for GLP compliance will depend upon the importance of the study to the overall risk assessment for the product and must be considered on a case-by-case basis.

For cell therapy products, core battery studies may include, but are not limited to, the following:

- a) tumourigenicity (*in vitro* and *in vivo* studies)
- b) biodistribution and engraftment studies
- c) ectopic tissue forming potential
- d) studies to support identification of safe/tolerable dose
- e) immunogenicity
- f) other tests specific to the nature of the product

CTAs should include evidence that the facilities performing pivotal pre-clinical studies have undergone inspection and audit by a designated GLP monitoring group.

The sponsor should provide a suitable scientific rationale to support the quality of the data generated from non-GLP compliant pre-clinical safety studies.

2.4.2.2 Using pre-clinical studies to assess key safety concerns

It is important to note that each cell therapy product will have its own inherent risk/benefit profile. Sponsors should adequately assess the potential safety concerns associated with their product and develop pre-clinical studies that clearly address these concerns in the context of the proposed treatment.

CTAs should include and discuss all safety data accumulated during pre-clinical assessment as well as a concise summary of how the evidence supports the products used in humans. Some of the risks that are commonly associated with cell therapy products, and which may be important to address during pre-clinical evaluation, are discussed below.

Researchers conducting pre-clinical studies to assess key safety concerns in animals need to balance the need to accumulate sufficient data with GLP principles related to reducing the number of animals used in testing. For this reason, efforts should be made to determine what studies have already been conducted and whether pre-clinical data may be appropriately obtained in *in vitro* or benchtop assays. In addition, animal pre-clinical study protocols can be planned to assess both key safety concerns discussed in this section as well as potential benefits discussed in Section 2.4.2.3.

Tumour formation

Some cell therapy products have been demonstrated to promote tumour formation. This risk is related to tissue source, cell type, and manufacturing process. Stem cells, for example, have been demonstrated to give rise to tumours following the introduction of specific gene mutations.

For manufacturing processes that involve cell culture, the potential for tumour formation may increase proportionally with the number of population doublings. The risk of spontaneous transformations, resulting in tumourigenicity, increases with the amount of time prior to differentiation, during prolonged culture (4 – 5 months) prior to transplantation. Genetic and epigenetic changes in cell lines, which accumulate over time, are likely to affect the capacity to differentiate and to induce/enhance tumour formation.

Pre-clinical data should not only address the potential for tumour formation, but also compare against and provide a sufficient understanding of normal cell proliferation rates and other factors that might result in an increase in transformation events.

Cells that are irradiated prior to clinical use may also require pre-clinical testing of tumorigenic potential.

Appropriate limits on cell culture duration or number of population doublings may be established, on the basis of the pre-clinical studies, and could help to manage risks associated with culture induced transformation events.

Immunogenicity

For the purpose of this guidance, immunogenicity can be broadly defined as the ability of the product to induce an immune response following administration. Immunogenicity can be influenced by various factors, including patient-/disease-related factors and product-related factors. This response is complex and can include antibody formation as well as other events such as T cell activation or innate immune response activation that could contribute to adverse responses. Immunogenic reactions can range in severity and type from local inflammation at the site of administration to severe allergic reaction or graft rejection. The potential for and degree of immune response should be assessed regardless of whether it is considered desirable or undesirable.

To properly address the immunogenicity for cell therapy products, pre-clinical studies should be completed using the final product formulation that is intended for clinical use, wherever possible. These studies may be done *in vitro* using the cell therapy product and human immune cells. Alternatively, these studies may require appropriate animal models, which may be immunosuppressed animals (in immune-competent animals) or immunodeficient animals. Potential effects at the site of clinical administration should also be tested in relevant animal models. Health Canada will consider the relevance of immunogenicity data developed using analogous cell therapy products made specifically for animals under sufficiently similar processes in preclinical studies on a case-by-case basis. Under these circumstances the analogous product should be supported by a sufficient rationale / evidence that the data produced using analogous cell therapy products can be considered relevant.

Ectopic tissue formation

Some cell therapy products have the capacity to differentiate into multiple cell types. The differentiation potential of such products differs depending on their type and the tissue micro-environment in which they reside following administration. Hence, there is a potential risk for cell therapy products to form unintended cell types (ectopic tissue) upon administration. The level of risk for ectopic tissue formation will need to be assessed on a case-by-case basis, but may be considered inherent for products derived from pluripotent stem cells.

Biodistribution and engraftment

A novel aspect of cell therapy products, compared to pharmaceuticals and other biologics, is the potential of cells to migrate throughout the body and reside (engraft) in

both target and non-target organs/tissues for long periods of time. As such, pre-clinical data regarding the biodistribution of cells after administration should be provided. It is recommended that sponsors determine both the level and duration of cell engraftment within both target and non-target tissues. In addition, the characterization of potential for formation of ectopic (unintended) cell types/tissues may also be of importance for certain cell therapy products. For products that are delivered systemically, particular attention should be paid to the lungs, which can provide a reservoir for cells and which are potential area for emboli formation.

Route of administration

Pre-clinical studies should directly address any potential risks that may arise due to the route of administration of the product. Potential risks may include, moderate to severe tissue damage, inflammation or acute loss of organ function. At a minimum, it is recommended that such studies be conducted in animal models using a relative dosage and route of administration that mimics, as closely as possible, the intended clinical situation. Justification should be provided for the pre-clinical study route of administration when different from the route of administration intended for CTA or for the dosage if significantly lower than the clinical dosage.

In the event that an authorised drug is proposed for use as an excipient, a DIN may not be sufficient to support a CTA, and further pre-clinical safety data may be required to support its use in a clinical trial.

2.4.2.3 Using pre-clinical studies to assess potential benefits

Pre-clinical studies should provide an in-depth assessment of potential benefits to support the product's clinical use. Studies should address the duration, magnitude and reproducibility of the effect. If possible, dose response relationships should be explored. In addition, effort should be made to understand the mechanism of action using model systems and assays that may provide insights for the development of product specifications and provide direction for clinical planning.

All efforts should be made to generate data in animal models that measure the effectiveness of cell therapy products for the proposed clinical indication under investigation. Health Canada acknowledges, however, that it may not be possible to use animal models for investigating the efficacy of cell therapy products for certain diseases. In such cases, suitable rationale must be provided to support the absence of efficacy testing in animals. Where appropriate, animal models that measure efficacy may also be used to generate additional pre-clinical information to support the safety of the cell product.

2.4.2.4 Establishing appropriate experimental models

The pre-clinical methods used for evaluating the risks and benefits associated with a cell therapy product will be highly dependent on the characteristics of the product and the

intended clinical use. It is the CTA sponsor's responsibility to establish and provide evidence/information to support the suitability of pre-clinical model systems. As such, the sponsor should provide clear rationale for the choice of model systems or assays utilized in pre-clinical studies. Both the benefits and limitations of each method should be concisely explained. If several methods are available, a rationale for the chosen methods should be provided. Guidance on identifying appropriate pre-clinical models for assessing the safety and efficacy of cell therapy products is provided below. Overall, the completion of studies in multiple model systems is encouraged and will provide a more accurate risk/benefit assessment to support clinical use of the cell therapy product.

Using in vitro and bench-top assays

While *in vitro* studies alone do not provide a sufficient mechanism for pre-clinical risk/benefit assessment, they can play a critical role in product characterization. Assays measuring the immunophenotype, viability, proliferative potential and functional characteristics of the cellular component can provide the basis for developing and measuring product specifications. The results of *in vitro* studies may also assist in the planning of pre-clinical studies in animals that will properly support clinical use of the product. The use of validated assays is recommended when generating pre-clinical data to support CTA submissions to Health Canada. In-house validation may be necessary where assays are not otherwise validated. Where in-house validation is used, the CTA sponsor should refer to methodology for validating analytical procedures described in ICH Q2(R1).

Using small animal models

Small animal models can provide insights into potential safety issues associated with cell therapy products as well as supporting information regarding efficacy. Immune-deficient rodents, in particular, provide an important mechanism for measuring tumour forming potential and the capacity of human cells to engraft, survive and differentiate in various tissues and organs. It should be noted, however, that the information obtained from small animal models may be of limited use and must be interpreted with caution in humans. Safety studies regarding biodistribution, the assessment of organ toxicities or adverse effects from direct administration may not necessarily extrapolate to the humans.

Using large animal models

Certain cell therapy product pre-clinical studies in large animal models may be warranted to better evaluate risk. Animals such as pigs, sheep and non-human primates, with body weights and organ sizes that resemble more those of humans, can provide important information on the risks associated with administration. They may also be useful in identifying a tolerable dose for early clinical investigation and for monitoring immunogenicity and tumour forming potential in an environment that more closely resembles the human situation.

Health Canada acknowledges that the use of large animal models has several challenges, including the potential need to develop a syngeneic equivalent of the human derived cell therapy product. In addition, the use of large animal models of disease may be difficult or, in some cases, unethical. The necessity for large animal models will be assessed based on the type and level of risks associated with the product's use in humans. Other justified or well described surrogate modelling could also be considered acceptable.

Animal studies should be well planned to help protect cell therapy clinical trial participants from potential risks, while avoiding unnecessary use of animals and other resources.

Germline Transmission

Some cell therapy products may have the capacity to contribute to germ cell formation. This is often dependent upon both cell type and mode of administration. The possibility for germ line transmission of product derived genetic material should be understood and addressed. This may be particularly important for pluripotent stem cell derived products.

2.4.3 Clinical Studies

Several guidance documents are available that provide information on the general principles and practices for the conduct of clinical trials. Many of these references are cited in Appendix B of this document and should be consulted by clinical trial sponsors.

The following sections will provide guidance that is specific for clinical trials involving cell therapy products.

2.4.3.1 Informed Consent and involvement of Research Ethics Boards

A CTA should contain contact information of the research ethics board that approved the protocol for each clinical trial site, and provide information about any research ethics board refusals to approve the protocol. While the research ethics board focus is on ethical issues related to the protocol (including substantive issues surrounding the informed consent process), Health Canada considers how the potential risks and anticipated benefits are communicated in informed consent forms as part of its CTA review. CTA sponsors must ensure that the risks associated with product are clearly and accurately stated and that potential benefits are not exaggerated.

Cell therapy CTA sponsors should be aware of ethical issues concerning the source of human derived materials and address these with the responsible research ethics board. Allogeneic donor informed consent is an important consideration and should be addressed adequately by cell therapy CTA sponsors. Donor consent procedures should outline any potential health risks associated with cell/tissue donation, and highlight for potential donors the importance of providing accurate information. It should also describe donor documentation retention requirements and the need to maintain traceability between donors and recipients. From a safety perspective, allogeneic donor

informed consent is an important consideration and should be addressed adequately by cell therapy CTA sponsors.

Some ethical issues unique to cell therapy products including donor informed consent processes and privacy issues do not fall under the federal mandate and may be addressed by professional practice standards / guidelines or organizations policies such as stem cell networks white papers or Canada's 2nd edition of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans or TCPS 2 (2014).

2.4.3.2 Designing Early Trials

Health Canada acknowledges that traditional first in human safety trials using cell therapies in healthy individuals may not be ethical because of inherent risks in cell transplantation. Instead, first in human trials for cell therapy products are likely to be completed in a subpopulation of patients for whom the treatment is intended. Decisions regarding the appropriate patient population for first in human trials must be determined based on careful consideration of both the benefits of the intended use and the potential risks associated with the product.

General clinical development guidelines for therapeutic products, or specific guidelines for the development of products to treat a particular condition, if available, should be followed.

Proof of principle and sound evidence of safety from pre-clinical studies, in well justified and relevant experimental and animal models, is necessary before the administration of cell derived products to humans. In situations where pre-clinical data is absent and/or not possible due to limitations discussed in Section 2.4.2.4, a first in human trial may still be considered acceptable if the sponsor can provide suitable justification that the clinical trial does not endanger the clinical trial subject, is not contrary to the best interests of the clinical trial subject, and the study objectives will be achieved.

Even in early clinical trials, uncertainty around long term safety of cell therapies should be addressed. Measures to identify and mitigate potential long term risks of study subjects should be discussed and carefully planned from the outset. Considerations for clinical trials in early stages of development are addressed together with later term stages of development under the heading "Monitoring and Follow-up".

The amount of clinical safety data accumulated from first in human studies is generally insufficient to adequately support product risk assessment. Subsequent early clinical trials to develop a basic safety profile for cell therapies may consist of tolerance or dose-range finding studies. The primary objective of such studies is to provide additional safety information with secondary objectives for exploring efficacy and/or determination of dose. Some cell therapy product specific issues that should be addressed when designing such trials are discussed below.

Establishing clinical dose

Traditional methods for defining the appropriate dose or dose range of a drug for testing in early clinical studies may not be applicable for certain cell therapy products. Confounding issues include the use of the product as add on therapy rather than monotherapy, the potential for long-term adverse effects associated with dose, and the lack of well-established methodologies for extrapolating pre-clinical data to the clinic setting. Appropriate dose must be determined on a case-by-case basis and should incorporate knowledge gained from all pre-clinical studies. In particular, studies that assess biodistribution and engraftment, tumour formation and immunogenic responses should be taken into account with emphasis on potential adverse reactions associated with high dose administration of the product. When possible, dose estimation should be based on previous clinical experience with similar cell types. Particularly where traditional methods for defining appropriate dose or dose ranges present challenges, sponsors are encouraged to use extrapolation, modelling, and/or simulation techniques that are supported by a scientific rationale and evidence.

In some cases, multiple administrations may be required to obtain intended and durable effects from a cell therapy product. In such cases, pre-clinical safety studies that mimic the proposed clinical administration methods may provide the best supportive evidence. When designing trials with multiple administrations, it is recommended that patients receive the same number of doses to allow meaningful comparison of endpoint data. For early multiple dose trials that utilize a placebo control arm, a cross-over design may be suitable. It should be noted, however, that such an approach requires a suitable “wash-out period” between administrations, which may not be feasible for some cell therapy products.

Pharmacodynamics/pharmacokinetics studies

Even if the mechanism of action is not well established or known in detail, efforts should be made in early clinical trials to understand the main therapeutic effects of the cell therapy product in humans. Knowledge from pre-clinical studies and any early clinical studies should be used to support the choice of the required duration of the follow-up for efficacy and safety. If the therapeutic effect is based on the replacement/repair of deficient or damaged cells/tissues, it may also be important to assess the function of the tissues, ideally using quantitative methods or a combination of quantitative and qualitative methods.

Traditional pharmacokinetic studies to assess biodistribution in humans may be challenging for cell therapy products and may require the development of appropriate cell tracking technologies. The presence of cells in non-target sites should be further investigated and the risks fully evaluated whenever feasible. Health Canada may insist on pharmacokinetic assessment for cell therapy products associated with higher risks of tumourigenicity or ectopic tissue formation prior to the initiation of trials in a large number of patients. Non-conventional methods that provide traditional pharmacokinetic

information would also be considered for determining dose and frequency, if an acceptable rationale is provided.

Proof of concept studies

After successful first in human and early safety studies have been conducted, proof of concept trials may be initiated early in clinical trial development to accumulate more product safety data, but with a primary endpoint focused on efficacy. Traditionally these trials recruit a greater number of patients than first in human or dose finding trials and are intended to provide sufficient information on the safety and benefits of the product to support the initiation of a pivotal efficacy trial in later development stages.

2.4.3.3 Designing Later Stage Trials

Building upon evidence accumulated from early stage clinical trials, later stage clinical trials aim to collect significant evidence of clinical safety and efficacy that may be considered pivotal to eventual market authorization. This generally requires longer term studies that are designed to enroll a suitable number of subjects to accurately assess product efficacy and risk compared to a standard of care or placebo group within the patient population that the drug is intended to treat.

Unique issues may be encountered during later stage clinical investigation of cell therapy products. Some of these issues are discussed in the sections below.

Statistical Considerations

While there may not be statistical issues that are specific to cell therapy products, a strong statistical plan is usually an indication of a well-designed trial. Careful choice of study endpoints, handling of multiplicity issues and discussion on strategies for controlling bias are all points that need to be taken into account when designing a trial. *Ad hoc* and *post hoc* analyses of data should be avoided when possible – these may provide some direction for future clinical study, but there are inherent difficulties in utilizing these analyses as direct evidence of clinical efficacy.

2.4.3.4 Clinical Efficacy Considerations

Clinical efficacy endpoints may include, but are not limited to physiological responses or changes in immune function, gene expression, or cell engraftment. The choice of endpoints, use of surrogate markers, appropriate control groups, trial duration and the potential need for long-term efficacy follow-up are all factors that must be considered when designing trials for cell therapy products.

2.4.3.5 Clinical Safety Considerations

The same principles used to investigate the safety of biologics should be applied when addressing safety considerations for cell therapy products. Issues that are more specific to cell therapy products include: graft failure, tumour formation, immune responses, ectopic

tissue formation, inflammatory events, viral activation and the distribution and engraftment of the cells throughout the body. Concerns specific to a product should also be addressed. These may include:

- lung emboli formation,
- respiratory and cardiac adverse effects and
- both local and systemic toxicities.

Safety considerations are often product and patient condition specific. When designing safety endpoints and monitoring adverse events it is important to carefully consider the body of knowledge accumulated on both the product being investigated, and similar cell therapy products, in the context of a given patient population.

2.4.3.6 Monitoring and Follow up

Longer than normal monitoring and follow-up periods should be included as part of clinical trial design for most cell therapy products. Determinations of the required length should include both efficacy and safety considerations. The precise length of time for monitoring will need to be tailored to the expected level of risk as governed by the type of product, the intended indication and the patient population. Long-term monitoring should be focused on survival and serious adverse events (e.g., oncologic, hematologic, immunologic, etc.). Detailed plans should also be put in place proactively to maintain long-term monitoring in cases of early stoppage. The need for validation of suitable surrogate end points should be considered.

Risks to donors of primary tissues, and risks to patients that are related to items on the following list should be considered when setting monitoring strategies and the period of duration for follow-up:

- product quality
- administration procedures
- biodistribution of the product
- long-term (potentially life-time) persistence of the product in the patient
- scaffolds, matrices and biomaterials (biodegradation)
- incompatibility of cell therapy with other drug products
- infectious disease transmission
- immunogenic reactions
- tumour or ectopic tissue formation
- multiple administrations
- storage and distribution of cell therapy
- potential unintended effects
- persistence of the intended effect in patients

2.4.3.7 Designing Trials for Rare, Life Threatening Indications

CTA sponsors may face challenges in obtaining sufficient evidence of safety and efficacy at various stages of clinical trial development for cell therapies for rare diseases or for life

threatening indications. For example, pivotal trials in a large patient population may not be possible at later stages of clinical development. Factors inhibiting development can include rare disease indications and/or an inability to generate sufficient product to treat a large number of patients. Thus, for some cell therapy products, proof of concept trials may be the only feasible mechanism for obtaining data to support product efficacy.

Health Canada remains available to discuss clinical trial development plans for cell therapies targeting small disease populations and life-threatening disease indications in pre-submission meetings. In addition, policy and regulatory mechanisms are in place to address these issues:

- Sponsors are referred to Health Canada's *Guidance Document: Notice of Compliance with Conditions (NOC/c)*.
- Health Canada's anticipated Orphan Drug Framework will provide regulatory support for sponsors pursuing treatments for rare disease indications.

2.4.3.8 Trial Risk Management

While medical care and medical decisions, in respect of the clinical trial, remain the responsibility of the supervising qualified investigator, CTA sponsors are encouraged to pro-actively develop clear stop-trial criteria to be followed during clinical investigations using cell therapies. These may be developed to describe how investigators can identify and address known and unknown potential safety risks.

In the event of a serious unexpected adverse drug reaction, the CTA sponsor is required to inform the Minister as per Part C, Division 5, Section C.05.014 of *the Food and Drug Regulations*. Further, the CTA sponsor has to notify Health Canada as per Section C.05.015 if the clinical trial is discontinued for any reason, including any safety concerns identified through adverse drug reactions.

APPENDIX A: CONTACT INFORMATION

Inquiries and information requests regarding this Guidance document and CTA submissions should be communicated to:

Office of Regulatory Affairs
Biologics and Genetic Therapies Directorate
Health Products and Food Branch, Health Canada
100 Eglantine Driveway, Address Locator
0601C Tunney's Pasture
Ottawa, Ontario K1A 0K9
Canada

E-mail: bgtd_ora@hc-sc.gc.ca

Telephone: (+1) 613-957-1722

Fax: (+1) 613-946-9520

Teletypewriter: 1-800-267-1245 (Health Canada)

Please note that the contact information is correct at the time of writing, and may change over time.

APPENDIX B: KEY HEALTH CANADA GUIDANCE DOCUMENTS

GENERAL GUIDANCE

- Guidance for Industry: Management of Drug Submissions
- Guidance Document: Preparation of Drug Regulatory Activities in the Common Technical Document (CTD) Format
- Guidance for Industry: Preparation of Drug Submissions in Electronic Common Technical Document (eCTD) Format
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications
 - Electronic Specifications for Clinical Trial Applications and Amendments filed in accordance with Guidance Document for Clinical Trial Sponsors: Clinical Trial Applications
- Guidance Document: Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used In Clinical Trials (GUI-0036)

QUALITY GUIDANCE

- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Conventional Biotherapeutic Products
- Guidance for Industry: Preparation of the Quality Information for Drug Submissions in the CTD Format - Biotechnological/Biological (Biotech) Products
 - Guidance for Sponsors: Lot Release Program for Schedule D (Biologic) Drugs

GLP GUIDANCE

- Guidance Document: Non-Clinical Laboratory Study Data Supporting Drug Product Applications and Submissions: Adherence to Good Laboratory Practice

GMP GUIDANCE

- Good Manufacturing Practices (GMP) Guidelines (GUI-0001)
- Annex 2 to the Current Edition of the Good Manufacturing Practices Guidelines - Schedule D Drugs (Biological Drugs) (GUI-0027)
- Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines - Drugs Used in Clinical Trials (GUI-0036)
- Guidance Document for Cell, Tissue and Organ Establishments – Safety of Human Cells, Tissues and Organs for Transplantation (2013)

APPENDIX C: REFERENCES

REFERENCES FOR QUALITY INFORMATION

International Conference on Harmonisation (ICH)

- ICH: Q1A(R2): Stability Testing of New Drug Substances and Products
- ICH: Q1C: Stability Testing of New Dosage Forms
- ICH: Q3C(R5) Guideline - Impurities: Guideline for Residual Solvents
- ICH Topic Q5C -Note for Guidance on Quality of Biotechnological Products: Stability Testing of Biotechnological / Biological Products.
- ICH: Q5D Guideline - Derivation and Characterization of Cell Substrates Used for the Production of Biotechnological/Biological Products
- ICH: Q5A(R1) Guideline - Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin
- ICH: Q6B Guideline - Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products
- ICH: Q9 Guideline - Quality Risk Management
- ICH: Q11 Guideline - Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities)

USP Chapters

USP <92> Growth Factors and Cytokines Used in Cell Therapy Manufacturing

USP <1043> Ancillary Materials for Cell-, Gene- and Tissue-Engineered Products

USP <1046> Cell and Tissue Based Products

REFERENCES FOR NON-CLINICAL AND CLINICAL INFORMATION

[OECD Principles of Good Laboratory Practice](#) [ENV/MC/CHEM(98)17]

International Conference on Harmonisation (ICH)

- ICH: S6(R1) Guideline - Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals
- ICH: E6 (R1) Guideline for Good Clinical Practice
- ICH E 11 Guideline – Clinical Investigation of Medicinal Products in the Pediatric Population

APPENDIX D: COMMON TECHNICAL DOCUMENT – MODULE 3 (QUALITY)

As a quick reference tool, sections in CTD Module 3 suggested for both upstream (i.e., biological starting materials) and downstream (i.e., drug substance/drug product) processes are **highlighted in grey** in the table below. Cell Therapy product-specific information in other CTD Modules than those suggested is acceptable.

CTD MODULE 3	
3	Quality
3.1	Table of Contents of Module 3
3.2	Body of Data
3.2.S	Drug Substance
3.2.S.1	General Information
3.2.S.1.1	Nomenclature
3.2.S.1.2	Structure
3.2.S.1.3	General Properties
3.2.S.2	Manufacture
3.2.S.2.1	Manufacturer(s)
3.2.S.2.2	Description of Manufacturing Process and Process Controls
3.2.S.2.3	Control of Materials
3.2.S.2.4	Controls of Critical Steps and Intermediates
3.2.S.2.5	Process Validation and/or Evaluation
3.2.S.2.6	Manufacturing Process Development
3.2.S.3	Characterization
3.2.S.3.1	Elucidation of Structure and other Characteristics
3.2.S.3.2	Impurities
3.2.S.4	Control of Drug Substance
3.2.S.4.1	Specification
3.2.S.4.2	Analytical Procedures
3.2.S.4.3	Validation of Analytical Procedures
3.2.S.4.4	Batch Analyses
3.2.S.4.5	Justification of Specification
3.2.S.5	Reference Standards or Materials
3.2.S.6	Container Closure System
3.2.S.7	Stability
3.2.P	Drug Product
3.2.P.1	Description and Composition of the Drug Product
3.2.P.2	Pharmaceutical Development
3.2.P.3	Manufacture
3.2.P.4	Control of Excipients
3.2.P.5	Control of Drug Product
3.2.P.6	Reference Standards or Materials

CTD MODULE 3	
3.2.P.7	Container Closure System
3.2.P.8	Stability
3.2.A	Appendices
3.2.A.1	Facilities and Equipment
3.2.A.2	Adventitious Agents Safety Evaluation
3.2.A.3	Excipients
3.2.R	Regional Information
3.2.R.1	Production Documentation
3.2.R.2	Medical Devices
3.2.R.3	Lot Release Documentation
3.2.R.4	Blood Establishment Data
3.3	Literature References



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