DRAFT GUIDANCE DOCUMENT Guidance for Sponsors: Preparation of Clinical Trial Applications for use of Cell Therapy Products in Humans

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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.

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" include 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 investigation 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 the following kinds of cell therapy products:

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

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 *Safety of Human Cells, Tissues and Organs for Transplantation Regulations* (*CTO Regulations)* provide a good basis for determining appropriate screening and testing for cell therapy products, although these CTO Regulations do not apply to these products. Any reduction in 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 safety and efficacy issues 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. Outstanding 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 = S*afety of Human Cells, Tissues and Organs for Transplantation Regulations*
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** Raw material from a biological source which is intended to be used in the fabrication of a drug and 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:** The final dosage form of a drug in the immediate packaging intended for marketing.
- **Drug substance:** 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:** The organizational process and the conditions under which laboratory studies are planned, performed, monitored, recorded, archived and reported.

- **Good Manufacturing Practices:** A defined system of determinants and controls for quality production, applicable to the manufacturing of drugs. 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.
- **Immunogenicity:** the ability of the product to activate either an innate (inflammatory) or cell mediated immune response following administration.
- **Impurity:** Any substance present which may arise during synthesis, purification and storage and considered to be different than the chemical composition of a desired material or compound which affects the purity of the desired material or compound.
- **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.
- **Quality Assurance:** 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:** Operational techniques and activities that are used to fulfil requirements for quality in compliance with the specification.
- **Raw Material:** Any substance, of biological origin (other than in-process drug (derived from the active substance) or packaging material, intended to be used in the manufacture of drugs, including those that appear in the master formula but that do not appear in the drug, such as solvents and processing aids.
- **Somatic cells:** any cells that have been differentiated (i.e. not stem cells or gametes).
- **Specification:** means a detailed description of a drug, the raw material used in a drug or the packaging material for a drug.
- **Starting Materials:** raw materials that are integral to the final product and often form the backbone from which the product is derived
- **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 information shall be submitted to Health Canada in a Clinical Trial Application (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 cellular 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 recognises 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 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 that investigate product efficacy in larger patient populations and may include pivotal trials.

Health Canada encourages sponsors to engage in pre-submission meetings 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.

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 appendices

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 C.02.019, C.02.025 and C.02,026). Certain sections of Division 2 only apply to imported drugs or to distributors that hold a Drug Identification Number. Cell therapies are expected to 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. 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.

Any CTA sponsors making changes to the manufacturing of a cell therapy product being investigated under an CTA is required to notify Health Canada in writing (in the event the change does not affect the quality of safety of the cell therapy) or in the form of a CTA-A (in the event that the amendment may affect the safety or quality of the drug).

2.3.1 CONTROL OF MATERIALS, REAGENTS AND EXCIPIENTS

Recommendation – Include information in

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

There are standard GMP requirements for the control of materials in drug production that are described in Division 2 of the *Food and Drug Regulations*. The testing of materials before use has three 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, and
- to provide assurance that the quality of the drug in dosage form will not be altered by variability in the materials

In addition, testing of materials ensures they are safe for the intended use.

2.3.1.1 Starting and Raw Materials

This section pertains specifically to starting and raw materials that are not of human or animal origin, which are discussed in Section 2.3.2 of this guidance.

Raw materials include any materials used in manufacturing that are procured from outside sources. As opposed to materials/reagents that are developed in house, whose quality is controlled through in process testing, the quality of procured materials is assessed according to GMP requirements. Starting materials are defined as raw materials that are integral to the final product and often form the backbone from which the product is derived. A component or formulation of the starting material is often found in the final cell therapy product to be administered to a patient.

In the case of cell therapies, raw materials (including starting materials) are often not GMP or pharmacopoeial grade. For such materials, in house quality control measures are required to mitigate the potential risks associated with their use. It is recommended that core safety tests be completed. At a minimum these should include assessment of sterility and endotoxin contamination. Other material tests should be put in place, when necessary, to characterize the critical aspects of safety and stability as well as suitability with respect to function in the manufacturing process.

For GMP or pharmacopoieal grade raw materials, up to date Certificates of Analysis should be provided, to verify the level of testing completed and the results provided by the manufacturer/supplier. The source of the materials should be indicated, where appropriate.

2.3.1.2 Ancillary Materials

Ancillary materials are defined as any reagent used in drug manufacturing that is not intended to be present in the final product. Cell therapy products are manufactured using a variety of unique and complex reagents, some of which may affect product efficacy or be associated with safety concerns if administered to patients. To mitigate these risks, ancillary materials must be appropriately qualified to assess source, purity, identity, safety and suitability.

In the early stages of cell therapy product development, ancillary material qualification programs 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.

Appropriate processes should be put in place to reduce the presence of ancillary reagents as much as possible. For potential high risk reagents, methods should be established to quantify their amount in the Drug Product and safety testing should be completed to evaluate potential adverse effects associated with these quantities.

2.3.1.3 Excipients

Excipients are manufacturing reagents that are intended to be present in the final Drug Product formulation. Those cell therapy products containing excipients of animal or human origin may be considered to possess a higher level of risk and a sufficient rationale should be provided for their use. In addition, animal or human excipients should meet all criteria discussed in Section 2.3.2 of this guidance on the Control of Human/Animal Derived Products for Manufacturing.

Controls must be in place to assess and mitigate the level of risk associated with the administration of the excipients to humans. The use of either pharmaceutical or clinical grade excipients is recommended as an appropriate mechanism to control risk. Use of non-pharmaceutical grade or non-clinical grade excipients shall be supported by an appropriate rationale. Quality control measures must be put in place to monitor the safety and quality of all excipients.

A therapeutic product sold on the Canadian market can be used as an excipient in a cell therapy product. Such excipients may be considered low risk and the product Drug Identification Number can provide a sufficient indication of safety and quality for use by a clinical trial sponsor. It should be noted that, when using a marketed therapeutic as an excipient, suitable evidence should be accumulated to demonstrate that any clinical effects are not due solely to the excipient itself. For, excipients marketed as therapeutic

products in other jurisdictions, but not in Canada, sufficient information must be submitted by the CTA sponsor to assess its quality and the associated risk of its proposed use in the proposed clinical trial.

2.3.2 CONTROL OF HUMAN/ANIMAL-DERIVED MATERIALS

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*

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. Specific regulatory submission requirements for human-sourced excipients, including any used in the placebo, are contained in C.05.005(*f*), which identifies the need for sufficient information to support the identity, purity, potency, stability and safety of these excipients. While there are inherent safety risks associated with the use of such materials; these risks can be appropriately mitigated though meticulous controls and testing. In particular, infectious diseases and TSE risks are addressed below.

2.3.2.1 Infectious Disease Screening and Testing Procedures

In products containing live cells, there is no opportunity for terminal sterilization before delivery. As such, the potential for transmission of infectious diseases through cell therapy products must be carefully addressed through appropriate controls. A combination of donor screening and testing is necessary to appropriately mitigate the risks of transmitting infectious diseases. Donor screening involves the completion of a medical and social history questionnaire and a physical examination. Donor testing involves the use of approved medical devices to detect relevant infectious disease agents or diseases. 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.

While it is the responsibility of manufacturers to adequately address risks of transmitting infectious diseases via their cell therapy products, the screening and testing described in *Guidance Document for Cell, Tissue and Organ Establishments - Safety of Human Cells, Tissues and Organs for Transplantation* can be used as a basic starting point for what Health Canada may consider acceptable (although the guidance is intended to address only basic human cells, tissues and organs for transplantation). Deviations from these screening and testing practices may be considered acceptable or may be required for logistical reasons or to better address safety, and a cell therapy CTA will be best supported by identifying and justifying any differences in donors screening or testing from the guidance document referenced above. In some cases it is expected the time frames for donor testing will be different for cell therapy products.

Challenges may be encountered when a cell therapy product will be manufactured using material from a cell or tissue bank that has not been screened or tested according to

screening and testing practices deemed to be acceptable to Health Canada. In this case, a CTA sponsor will need to consider options such as re-screening and re-testing donors (perhaps using stored aliquots). Alternatively, the CTA sponsor may propose an alternate method that adequately mitigates the risk or provide additional evidence to satisfy Health Canada that the risk is sufficiently small and that the clinical trial is still in the best interests of the clinical trial subjects (for example, by showing how the processing adequately reduces the risk).

In cases where materials are obtained from other establishments, such as blood or tissue banks, evidence of current registration under the appropriate regulatory jurisdictions must be provided, along with evidence and attestation that cell/tissue donors were appropriately screened and tested according to standards deemed acceptable by Health Canada. Where materials are collected outside Canada, information may be required to establish that they were collected under regulatory requirements equivalent to Health Canada's.

Donor screening and testing may not always be required for donors of autologous cell therapy products. However, a certain level of infectious disease testing is recommended to identify and prevent potential cross-contamination of products. Where infectious disease testing is not performed or inadequate, a detailed description of measures to prevent cross-contamination must be provided

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 cellular 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.

2.3.3.2 Process Validation

In early clinical stages only minimal process validation is expected 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 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 is the active ingredient that is intended to furnish pharmacological activity. 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 are required in the Drug Submission Template in CTD format may not be achievable, or appropriate. In such cases where a clear rationale can be provided, it is not necessary to identify and submit quality and manufacturing information pertaining to a DS. Instead, any relevant DS sections that are not specifically covered in the DP sections can be combined with the DP section.

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. It is acknowledged 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 also be performed as in process controls and as close to the DP as possible.

Health Canada understands that the development of specifications based on pre-clinical data may be difficult in the early stages of drug development. As such 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.

Analysis of several product batches is encouraged as a measure of process variability. 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. 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 complete 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 enrolled in the study and how the manufacturing process may be affected by such differences. The accumulation of this knowledge may require an initial comparator study of product derived from healthy and affected donors.

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.

The processes for manufacturing cell therapy products may generate several types of impurities, *i.e.;*

- non-viable cells
- cell types that do not contribute to the mechanism of action for the drug
- tumourigenic cells
- cell substrate-derived impurities (*e.g.* host-cell proteins and DNA)
- ancillary materials
- adventitious agents

Such process-related impurities may be related to safety concerns, such as; toxicity; oncogenicity; 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 Q2B).

2.3.4.5 Adventitious Agents

The nature of cell therapy product manufacturing processes is particularly amenable to the introduction of adventitious agents. 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. 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 can also be a source of potential 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.

It is important that at least one sample from each DP lot is tested for the presence of adventitious agents whenever possible. For directed allogeneic or autologous products, a complete 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.

The absence of adventitious agent testing prior to patient administration will need to be well rationalized.

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 during the 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, cell number and viability of product 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 encompass all expected extremes when practicable.

Stability studies should be extended throughout the product life-cycle to encompass any changes in the manufacturing or storage and transportation processes. When possible, stability studies should include any new product specifications as they become introduced; 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 they run contrary to GCP, and in particular if (A) the use of the cell therapy for purposes of the clinical trial endangers the health of clinical trial subject, or (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 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, 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 recommended 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 such pre-clinical evidence from Canadian studies or studies conducted outside Canada based on its scientific merit. In addition, pre-clinical studies can establish scientific rationale to support clinical utility. General guidance on pre-clinical safety studies can be found in *ICH Topic S6 (R1): Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

2.4.2.1 The importance of Good Laboratory Practices (GLPs)

Pre-clinical studies that are considered pivotal for risk evaluations must adhere to 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, pivotal or 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 must 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 use 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.

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 stem 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.

Cell irradiation also has the potential to induce tumourigenic transformation events. As such, cell lines that are irradiated prior to therapeutic use may also require pre-clinical testing of tumourigenic potential.

Appropriate limits on the 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 affect (positively or negatively) either an inflammatory or cell mediated immune response following administration. Immunogenicity can arise from the cells themselves, such as graft rejection from allogeneic-derived products, or from ancillary materials present in the final product. 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. Potential effects at the site of clinical administration should also be tested in relevant animal models.

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 extremely high 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 is a 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 if the route of administration for pre-clinical studies differs from the intended clinical route or if the dosage is significantly smaller than the intended 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 products 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.

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 Q2B

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 that can be provided 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 human situation.

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.

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 A 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

A CTA must 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. From a federal government perspective, CTA sponsors must ensure that the risks associated with product are clearly and accurately stated and that potential benefits are not exaggerated.

In addition to clinical trial participant informed consent, 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. From a safety perspective, 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.

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 Tri-Council Policy Statement.

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 proceed 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 further may consist of tolerance or dose-range finding studies with the experimental agent used as monotherapy or add-on to another agent. 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 potential for long-term adverse effects associated with dose and a lack of 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.

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 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 cell therapy product derived 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.

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 focussed 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 enrol a suitable number of subjects to accurately assess product efficacy and risk compared to a standards 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 we designing a trial. *Adhoc* and *post hoc* analyses of data should be avoided when possible - these may provide some direction for future clinical study, 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 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 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 focussed 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.

The following should be considered when setting monitoring strategies and the period of duration for follow-up:

- Risks to living donors of primary tissues.

- Risks to patients related to product quality.
- Risks to patients related to administration procedures.
- Risks related to biodistribution of the product.
- Risks related to long-term (potentially life-time) persistence of the product in the patient.
- Risks related to scaffolds, matrices and biomaterials (biodegradation).
- Risks related to incompatibility with other drug products.
- Risks of infectious disease transmission.
- Risks related to multiple administrations.
- Risks associated with storage and distribution.
- Risk of immunogenic reactions.
- Risk of tumour or ectopic tissue formation.
- Risks of 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 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 shall report to the minister as required under Part C, Division 5, Section C.05.014 of *the Food and Drug Regulations*. The CTA sponsor will further report under 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
200 Tunney's Pasture Driveway, Address Locator 0700A
Tunney's Pasture
Ottawa, Ontario K1A 0K9

E-mail: bgtd_ora@hc-sc.gc.ca
Telephone: 613-957-1722
Fax: 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 Sponors: 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)
- 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

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
3.2.P.7	Container Closure System
3.2.P.8	Stability

CTD MODULE 3	
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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