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NATIONAL PHARMACEUTICAL REGULATORY AGENCY
MINISTRY OF HEALTH MALAYSIA

GUIDANCE DOCUMENT AND GUIDELINES FOR REGISTRATION OF CELL AND GENE THERAPY PRODUCTS (CGTPs) IN MALAYSIA

Second edition (September 2025)

National Pharmaceutical Regulatory Agency
Ministry of Health Malaysia

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- **Malaysian Dental Council (MDC)**

SOME CONTENTS IN THIS DOCUMENT HAVE BEEN EXTRACTED FROM THE FOLLOWING REFERENCES:

1. Guidance for industry: Guidance for human somatic cell therapy and gene therapy (US FDA)
2. Guideline on human cell-based medicinal products (EMEA/CHMP/410869/06) (EMA)
3. Reflection paper on classification of ATMPs (EMA)
4. Guidance for industry and FDA Staff: Minimal manipulation of human cells, tissues, and cellular and tissue-based products (US FDA)
5. Annex 2 Manufacture of biological medicinal substances and products for human use, PE 009-11 (Annexes) (PIC/S)
6. Guidelines for the clinical translation of stem cells (ISSCR)
7. Moore WA and Bermel J. Cell therapy manufacturing (Bioprocess International)
8. Lee MH, Au P, Hyde J, *et al*. Translation of regenerative medicine products into the clinic in the United States: FDA perspective (Translational Regenerative Medicine, 2015)
9. MACT. About Malaysian Cell Therapy Patient Registry (MCTPR). Available at: https://mact.org.my/reg_about_mctpr.html .

ABBREVIATIONS

ACTD	ASEAN Common Technical Dossier
BWP	Biologics Working Party
CMC	Chemistry, Manufacturing and Controls
CHMP	Committee for Medicinal Products for Human Use
CDCR	Control of Drugs and Cosmetics Regulations
CGTP(s)	Cell and Gene Therapy Product(s)
CT	Cellular Therapies
CTIL	Clinical Trial Import Licence
CTP(s)	Cell Therapy Product(s)
CTX	Clinical Trial Exemption
DCA	Drug Control Authority
DNA	Deoxyribonucleic Acid
ERA	Environmental Risk Assessment
EU	European Union
EMA	European Medicines Agency
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GTP(s)	Gene Therapy Product(s)
hESCs	human embryonic stem cells
HSC	Haematopoietic Stem Cells
HTA	Health technology assessment
ICH	International Conference of Harmonisation
iPSCs	induced Pluripotent Stem Cells
IND	Investigational New Drug
INN	International Non-proprietary Names
MCB	Master Cell Bank
MVS	Master Virus Seed
MOH	Ministry Of Health
MSCs	Mesenchymal Stromal/Stem Cells
NPRA	National Pharmaceutical Regulatory Agency
PK/PD	Pharmacokinetic/ Pharmacodynamic
Ph. Eur.	European Pharmacopeia
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PBRER	Periodic Benefit Risk Evaluation Report
PSUR	Periodic Safety Update Reports
QC	Quality Control
QWP	Quality Working Party
RM	Regenerative Medicines
SC	Stem cells
TSE	Transmissible Spongiform Encephalopathies

US FDA	United States Food and Drug Administration
RMP	Risk Management Plan
WCB	Working Cell Bank
WVS	Working Virus Seed
WHO	World Health Organisation

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1. INTRODUCTION

Intensified research in the field of regenerative medicine (RM) over the last decades have accelerated our understanding of stem cell biology, and developmental, morphological and physiological processes that govern tissue and organ formation, maintenance, regeneration and repair following injuries. Although there are still gaps in current scientific knowledge, early concepts of cell therapy have been successfully translated into clinical practice. The utilisation of bone marrow transplants for haematological malignancies has been practiced for almost half a century. In addition to stem cells from the embryos, foetal tissues, amniotic membrane and umbilical cord, some multipotent adult stem cells have been identified within specific niches in human tissues and organs (e.g. bone marrow, heart, adipose tissues).

Stem cell-based therapies offer the possibility to restore damaged or lost cells. In addition, the use of genetically modified stem cells as delivery vehicles also offers great promise in correcting inherited genetic defects. Nevertheless, the development of Cell and Gene Therapy Products (CGTPs) present unique regulatory challenges different from traditional biotechnology and biopharmaceuticals, some of which are listed as follows:

- Unlike biotechnology products which are mostly purified proteins of cells, CGTPs contain living and functional cells
- The boundary-crossing nature of CGTPs are subject to a wide variety of regulatory oversights to encompass product development and administration in the clinical setting
- The use of CGTPs poses some difficult-to-appraise risks, such as tumorigenicity, immunogenicity, *in vivo* migration of transfused cells and reversibility of administration in the event of an intolerable reaction
- In addition to the requirements of Good Manufacturing Practice (GMP), the principles of Good Tissue Practice need to be applied in the quality assurance of a CGTPs.

In consideration of the unique challenges of CGTPs regulation mentioned above, the Malaysian CGTPs regulation framework has been formulated based on sound science and international best practices modelled from benchmarked regulatory authorities. It applies several levels of regulation on products based on the risks associated with their use. The framework also allows some flexibility in accommodating emerging RM technologies.

In summary, this guidance document is intended to guide the development and assessment of CGTPs in Malaysia. As scientific knowledge and technology in RM are still maturing, this will serve as a living document, evolving further in line with

updates in scientific knowledge and experience. It is hoped that accrued experience in CGTPs registration will allow NPRA to optimally match its guidelines and policies to the genuine risks and benefits associated with CGTPs. Ultimately, we aim for a safe and effective translation of novel cellular and gene therapies for numerous genetic and degenerative disorders in humans.

2. REGULATORY FRAMEWORK

2.1 LEGAL BASIS

As Cell and Gene Therapy Products (CGTPs) are presented as having properties for medical purposes – treating or preventing diseases in human beings, or that they may be used in or administered to human beings with a view of restoring, correcting or modifying physiological functions by exerting principally pharmacological, immunological or metabolic action, they are classified as products. CGTPs fit within the meaning of products under the **Sale of Drugs Act 1952: Control of Drugs And Cosmetics Regulations 1984** and would be classified as biological products. Thus, the essential aim is to safeguard public health through assurance of products' quality, efficacy and safety.

This document is consistent and integrated with the existing legislative framework. Hence, it should be read in conjunction with the relevant provisions of the **Control of Drugs and Cosmetics Regulations 1984 (CDCR 1984)** and the relevant sections of other applicable NPRA guidance documents and guidelines, as listed below (available at https://www.npra.gov.my):

a. Drug Registration Guidance Document (DRGD), including Guidelines on Registration of Biologics, DRGD (Appendix 4)
b. Guideline for the Submission of Analytical Method Validation (AMV) Documents (NPRA)
c. Malaysian Guideline for Good Clinical Practice (MOH)
d. Malaysian Variation Guideline for Pharmaceutical Products (NPRA)
e. Malaysian Variation Guideline for Biologics (MVGB) (NPRA)
f. Guidance Document on Foreign GMP Inspection (NPRA)
g. Guidance Note for Cell and Gene Therapy Products (CGTPs) Manufacturing Facility in Malaysia (NPRA)
h. Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption (NPRA)
i. Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holder (NPRA)
j. The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use (ASEAN)
k. Guideline on Good Distribution Practice (NPRA)

In addition, the boundary-crossing nature of many of the CGTPs and applications are subject to a wide variety of regulatory oversights. Thus, the following Ministry of Health (MOH), Malaysia Acts and Guidelines are also applicable and complement the CGTPs regulatory framework:

a. Poisons Act 1952 (Act 366)
b. Private Healthcare Facilities and Services Act 1998 (Act 586)
c. Guidelines For Stem Cell Research And Therapy
d. National Standards For Stem Cell Transplantation
e. National Guidelines For Haematopoietic Stem Cell Therapy
f. National Standards For Cord Blood Banking And Transplantation
g. Checklist For Research On Stem Cell and Cell-Based Therapies (NSCERT)
h. *Garis Panduan Pengimportan dan Pengeksportan Tisu Manusia atau Mana-mana Bahagiannya: Bahagian Kawalan Penyakit*
i. Medical Device Act 2012 (Act 737)
j. Biosafety Act 2007 (Act 678)
k. Dental Act 2018 (Act 804)
l. Medical Act 1971 (Act 50)

The CGTPs guidance document and guidelines for registration was developed based on similar fundamental concepts and scientific principles of established international regulatory framework. Hence, the document should be read in conjunction with other relevant/ applicable international guidelines referenced in this document. One may refer to *REFERENCES ON CGTPs REGULATION* **at the end of the document** for other relevant guidelines by World Health Organization (WHO), International Conference on Harmonisation (ICH), United States Food and Drug Administration (US FDA), European Medicines Agency (EMA), Therapeutic Goods Administration (TGA) and etc.

2.2 ABOUT THIS FRAMEWORK

The regulatory framework aims to provide a clear and predictable pathway for CGTPs based on internationally benchmarked regulations. NPRA strives to emulate the examples set by better established regulatory authorities such as those cited above, thus it has deemed that it shall not “reinvent the wheel”, rather adopt and adapt the regulatory guidance and guidelines from these agencies as appropriate for local use.

This document provides information for manufacturers, applicants, healthcare professionals and the general public on legal arrangements in Malaysia for the registration CGTPs.

This framework lays down specific rules on registration and its data requirements [Chemistry, Manufacturing Control (CMC), nonclinical and clinical], supervision, Risk Management Plan (RMP) and pharmacovigilance of CGTPs.

The cross-boundary nature of CGTPs involves a multidisciplinary approach; therefore, its full control will also be subject to various other regulations (authorities), hence an integrated oversight is imperative, as follows:

a. The clinical use/ medical procedure of the product will be under the ambit of Medical Development Division of the Ministry of Health, Malaysia
b. The private healthcare facilities and services (PHFS) will be under the Medical Practice Division of the Ministry of Health, Malaysia
c. The medical practitioners are regulated by the Malaysian Medical Council (MMC) while dental practitioners are regulated by the Malaysian Dental Council (MDC)
d. The device element of such products must comply with the Medical Device Act and regulations under the ambit of Medical Device Authority (MDA) of Malaysia, and
e. NPRA will ensure the product's quality, efficacy and safety.

For combination product (drug/ device, biological/ device, or drug/ device/ biological), only one agency (NPRA/ MDA) function as the primary agency for the registration of the combination product, based on the primary mode of action/ the principal mechanism of action by which the claimed effect or purpose of the product is achieved.

a. Drug is based on pharmacological, immunological or metabolic action in/ on the body; shall be regulated by NPRA;

b. Medical device does not achieve its primary mode of action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its intended function by such means (eg. mechanical action, physical barrier, replacement of or support to organs or body functions); shall be regulated by MDA.

Refer Table I: Medical Device-Drug-Cosmetic Interphase (MDDCI) and Combination Products Classification Decision in *Appendix 2, DRGD for examples of Drug-Medical Device/Medical Device-Drug Combination Product classification*.

Prior to registration, an applicant may apply for classification to NPRA through product classification form which is available at www.npra.gov.my.

The framework is based on a risk-management system approach, i.e. different levels of regulations are applied to CGTPs based on the risks associated with their use. Applying the risk-based approach throughout all stages of a product's lifecycle, from conceptualisation through tissue selection and collection, to its release and clinical use is essential for ensuring optimum product quality, efficacy and safety.

2.3 GUIDING PRINCIPLES

The primary objective of CGTPs regulation is to safeguard public health and patient safety. CGTPs should meet the same stringent standards on quality, safety and efficacy, as of any other biological products. In regulating CGTPs, we undertake a cautious science-based approach balanced against mitigating unnecessary administrative costs to the product developer.

Finally, our experience demonstrates that a transparent and open dialogue with all relevant stakeholders is the key to put in place a robust and pragmatic regulatory framework in this emerging field whilst promoting a patient-oriented, innovative and favourable regulatory environment.

3. SCOPE

This multidisciplinary guideline will address development, manufacturing and quality control as well as nonclinical and clinical development of CGTPs which include cell therapy, tissue engineering and gene therapy products as defined in this document. This guideline is intended for products entering the registration process at NPRA. However, the principles laid down in the guideline should be considered by applicants entering into clinical trials as well.

Cellular-based products discussed in this document have the following characteristics:

a. They contain viable human cells of allogeneic or autologous origin undergoing a manufacturing process
b. They may be combined with non-cellular components
c. The cells may be genetically modified

Product containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

Although this document does not cover non-viable cells and cellular fragments originating from human cells, the underlying scientific principles may be applicable if the manufacturing process of a CGTPs involves their use.

The following are **included** in the framework:

a. Human stem cells
b. Human tissue therapy products (e.g. skin, cardiovascular, ocular, musculoskeletal tissues)
c. Human cellular therapy products (e.g. cartilage cells, pancreatic islet cells, cultured skin cells, haematopoietic stem/ progenitor cells derived from peripheral and cord blood)
d. Genetically modified cellular products.
e. Cell-based cancer vaccines and cell-based immunotherapies
f. Dendritic cells, lymphocyte-based therapies, cell-based therapies for cancer, peptides and proteins.

The following are **not included** in the framework:

a. Fresh viable human organs, or parts of human organs, for direct donor-to host transplantation.
b. Fresh viable human haematopoietic stem/ progenitor cells for direct donor to-host transplantation for the purpose of haematopoietic reconstitution.
c. Labile (fresh) blood and blood components (e.g. fresh frozen plasma, platelet rich plasma)
d. Unprocessed tissues including reproductive tissues (e.g. sperm, eggs, embryos for *in vitro* fertilization (IVF) and other assisted reproductive technology procedures)
e. Secreted or extracted human products (e.g. milk, collagen)
f. Samples of human cells or tissues that are solely for diagnostic purposes in the same individual
g. *In vitro* diagnostic devices
h. Established therapy standard of care (S) listed in the National Guidelines for Haemopoietic Stem Cell Therapy
   (Directive Bil 19 year 2020: https://www.npra.gov.my/index.php/en/directive-general/1527171-direktif-berkenaan-pelaksanaan-pendaftaran-produk-dan-penguatkuasaan-secara-berperingkat-bagi-produk-terapi-sel-dan-gen-cgtps-serta-tambahan-senarai-produk-di-luar-skop-kawalan-cgtps-oleh-pbkd.html)
i. Prophylactic vaccines for infectious diseases (e.g. mRNA, plasmid DNA, or viral-vectored vaccines)
j. Cell or tissue lysates, extracellular vesicles and secretomes

The inclusion and exclusion lists are not self-contained. The lists may be amended as required.

Products indicated for general well-being, cosmetic/aesthetic purposes (anti-aging) and rejuvenation are not allowed unless they are intended for a medicinal purpose and substantiated by clinical studies with appropriate and clearly defined endpoints to demonstrate efficacy and safety.

For CGTPs indicated in rare diseases, an application for Orphan Medicines status can be submitted to NPRA. Please refer to the *Appendix 13, Designation and Registration of Orphan in Drug Registration Guidance Document (DRGD) for more information*.

4. DEFINITIONS

4.1 CELL THERAPY PRODUCTS

Cell therapy products are treatment that involves living cells to repair, replace or regenerate damaged tissues or treat diseases. These can be classified into several categories based on the type of cells used and their therapeutic application. Some common cell therapy product includes somatic cell, stem cell, and immune cell.

The guideline is relevant to all products using stem cells as starting material. The final product may consist of terminally differentiated cells derived from stem cells, or undifferentiated stem cells, or even a mixture of cells with varying differentiation profiles.

Somatic cell therapy is the administration to humans of autologous, allogeneic, or xenogeneic living non-germline cells, other than transfusable blood products for the purpose of treating, preventing or diagnosing a disease.

Cells can be self-renewing stem cells, more committed progenitor cells or terminally differentiated cells exerting a specific defined physiological function.

Stem cells (SC) are natural occurring cells in the body that have the ability to divide and produce a range of different cell types, pertinent to growth and repair after an injury.

For the purpose of this document, stem cells include the following:

a. Embryonic stem cells
b. Adult or somatic stem cells
    i. Haematopoietic progenitor/ stem cells (HSCs);
    ii. Mesenchymal stromal/ stem cells (MSCs)
    iii. Tissue-specific progenitor/ stem cells

c. Induced pluripotent stem cells (iPSCs)

Embryonic stem cells are pluripotent and have the capacity to differentiate to virtually every cell type found in the human body. Human embryonic stem cells (hESCs) can be characterised by a distinct set of cell surface markers, as well as marker genes for pluripotency. hESCs, when transplanted into a permissive host form teratomas, benign tumours consisting of various cell types derived from all three germ layers; endoderm, mesoderm and ectoderm. hESCs can be differentiated *in vitro* using either external factors in the culture medium, or by genetic modification. *In vitro* differentiation can generate cell populations with varying degree of heterogeneity.

Haematopoietic stem cells (HSCs) are a specific class of tissue-specific stem cells. They can give rise to differentiated cells of all haematopoietic lineages, myeloid and lymphoid, either in the haematopoietic bone marrow or in the thymus. These stem cells are also found in the placental and cord blood at birth in concentrations similar to levels found in adult bone marrow. In the adult body, HSCs are localised in the red bone marrow and found circulating at a lower frequency in the peripheral blood. They may also be found at low frequency in other tissues (liver, spleen and muscle) but their origin and relevance for normal haematopoiesis remains to be fully determined. HSCs are mobilised to the blood compartment after treatments with intensive chemotherapy and/or growth factors.

Mesenchymal stromal/ stem cells (MSCs) are primarily derived from bone marrow stroma or adipose tissue. Additionally, MSCs have been isolated from numerous other tissues, such as retina, liver, gastric epithelium, tendons, synovial membrane, placenta, umbilical cord and blood. MSCs are defined by adherence to plastic, specific surface antigen expression and multipotent differentiation potential. They are lineage-committed cells as they can differentiate towards mesenchymal lineages, mainly adipogenic, osteogenic and chondrogenic cell lineages. Under appropriate culture conditions *in vitro* differentiation to tenocytes, skeletal myocytes, astrocytes and neurons has been described.

Tissue-specific progenitor/ stem cells have a limited differentiation capacity and normally produce a single cell type or a few cell types that are specific to that tissue (e.g. tenocytes, myocytes, astrocytes).

Induced pluripotent stem cells (iPSCs) are artificially generated stem cells. They are reprogrammed from somatic adult cells such as skin fibroblasts to reacquire both the stemness and differentiation capacity of self-renewing embryonic stem cells. iPSCs share many features of hESCs; they have self-renewing capacity, are pluripotent and form teratomas. Increasingly iPSCs are being produced from different adult cell types. Their differentiation capacity seems to be dependent on

the cell type and age of the cells from which the iPSCs were reprogrammed. There is a current knowledge gap with respect to alterations of cell-specific regulatory pathways, differences in gene expression and in epigenetic control. These characteristics may result in tissues chimerism or malfunctioning of the cells.

4.2 GENE THERAPY PRODUCTS

A gene therapy product means a biological product:

a. which contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and
b. its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of gene expression of this sequence.

Gene therapy products shall **not include**:

a. vaccines against infectious diseases
b. chemically synthesised nucleic acids (e.g. RNA, DNA, oligonucleotides)

The final product may contain as an integral part of a medical device or an active implantable medical device.

When the genetic manipulation is *ex vivo* on cells that are then administered to the patient, this is also a type of cell therapy or also known as gene-modified cellular products and must adhere to regulatory guidelines set forth for both gene therapy and cell therapy products.

NOTE:

i) A chemically synthesised nucleic acid is synthesised from relatively short fragments (building blocks) of nucleic acids with defined chemical structure. The fragments are sequentially coupled to the growing oligonucleotide chain in the order required by the desired sequence of the product. Synthetic nucleic acids are typically single-stranded DNA or RNA molecules around 15–25 bases in length.
ii) A recombinant nucleic acid contains a sequence usually consisting of combination between original nucleic acids with foreign nucleic acids; where foreign nucleic acids are usually synthesised and amplified through polymerase chain reactions (PCR).

4.3 COMBINATION PRODUCTS

A combination product means it must incorporate, as an integral part of the product one or more medical devices. Its cellular or tissue part must contain viable cells or non-viable cells that act upon the human body with an action that can be considered as primary to that of the devices referred to.

A product can be composed of different categories of regulated articles: Device-biologic, biologic-drug-device (not biologic-biologic, etc). They can be physically or chemically combined, co-packaged or packaged separately but cross-labelled.

Products containing both a somatic cell component and another drug or device component in the final product will be considered and managed as combination products.

Please refer to the *Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products, and Appendix 2 of Drug Registration Guidance Document (DRGD),* for more information.

4.4 CELL-BASED IMMUNOTHERAPY

Cell-based immunotherapy aims at treating patients by stimulating their immune system using autologous or allogeneic cells. Immunotherapy of cancer is based on an immune response targeted against tumour-specific/tumour associated antigen(s), leading to destruction of malignant cells. The targeting of interactions between the immune system and the tumour constitute a complex approach of which the precise mechanisms of action are often not fully understood.

In the scientific literature, cell-based immunotherapy products for the treatment of cancer are sometimes called cell-based tumour vaccines or cell-based cancer vaccines.

This guidance document covers viable cell products for cancer-immunotherapy from autologous or allogeneic origin, consisting of e.g. whole tumour cells or autologous dendritic cells loaded with tumour antigens, all intended to induce tumour-specific cytotoxicity although the immunological pathway may differ between products. Tumour-specific cells intended for adoptive transfer (i.e. passive immunisation strategies) are also included, for example *ex-vivo* primed T-cells. Some principles outlined in this document may also be applicable to tumour cell lysates.

The cells may be chemically treated or genetically modified *in vitro* to immortalise them or to express certain gene products like growth factors or tumour antigens. If the product is to be considered as a gene therapy product, further guidance can be found in the EMA Guideline on the quality, non-clinical and clinical aspects of gene therapy products.

5. RISK ANALYSIS OF CELL AND GENE THERAPY PRODUCTS (CGTPs)

“Risk” is defined as “a potential unfavourable effect that can be attributed to the clinical use of CGTPs and is of concern to the patient and/or to other populations (e.g. caregivers and offspring)”.

“Risk factors” are defined as “qualitative or quantitative” characteristics that contribute to a specific risk following handling and/or administration of CGTPs”. Aspects that should be taken into account when identifying risk factors include, but are not limited to: origin of cells or tissues (autologous vs. allogeneic), ability of cells to proliferate and differentiate, ability to initiate an immune response (as target or as effector), level of cell manipulation (*in vitro/ex vivo* expansion, activation, genetic manipulation), aspects of manufacturing process, non-cellular components, mode of administration (*ex vivo* perfusion, local, systemic) and duration of exposure (short-term or permanent). In addition, the use of products that are “banked, transported, or processed in facilities with other cellular or tissue-based products” increases the risk of contamination or damage and may affect the infectivity, virulence, or other biologic characteristics of adventitious agents in the tissue. Furthermore, the clinical use of the CGTPs should be considered when identifying risk factors. Patient-, disease-, and medical procedure-related risk factors may contribute to the specific risks associated with a CGTP.

The risk-based approach is defined as a strategy aiming to determine the extent of quality, nonclinical and clinical data to be included in the registration dossier, in accordance with the scientific guidelines relating to the quality, safety and efficacy of the products.

For the purpose of classification and control of cell therapy products in this framework, **processing** is defined as any activity performed other than recovery, donor screening, donor testing, storage, labelling, packaging, or distribution, such as testing for microorganisms, preparation, sterilisation, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

With regards to processing, the terms “minimal manipulation” is defined as follows:

Minimal manipulation means:

a. For **structural tissue**: processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair or replacement
b. For **cells or non-structural tissue**: processing that does not alter the relevant biological characteristics of cells or tissues.

The following processes are generally considered as minimal manipulation: cutting, grinding, shaping, centrifugation (including the addition of an appropriate anticoagulant), soaking in antibiotic or antimicrobial solutions, sterilisation, irradiation (depending on dose), cell separation/concentration/purification, filtering, lyophilisation, freezing, cryopreservation, vitrification. It should be pointed out that this list is non-exhaustive, and any other manipulations can be considered as minimal manipulation, based on scientific considerations.

Examples of substantial manipulation are cell expansion (culture), genetic modification of cells, and differentiation with growth factors. If information does not exist to show that the processing meets the definition of minimal manipulation, the processing will be considered to be "more than minimal manipulation".

Typically, minimally manipulated products require less burdensome characterisation and control than cell products subjected to extensive manipulations *ex vivo.*

Cells and tissues are considered **'**engineered' if they have been subjected to substantial manipulation, so that their biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.

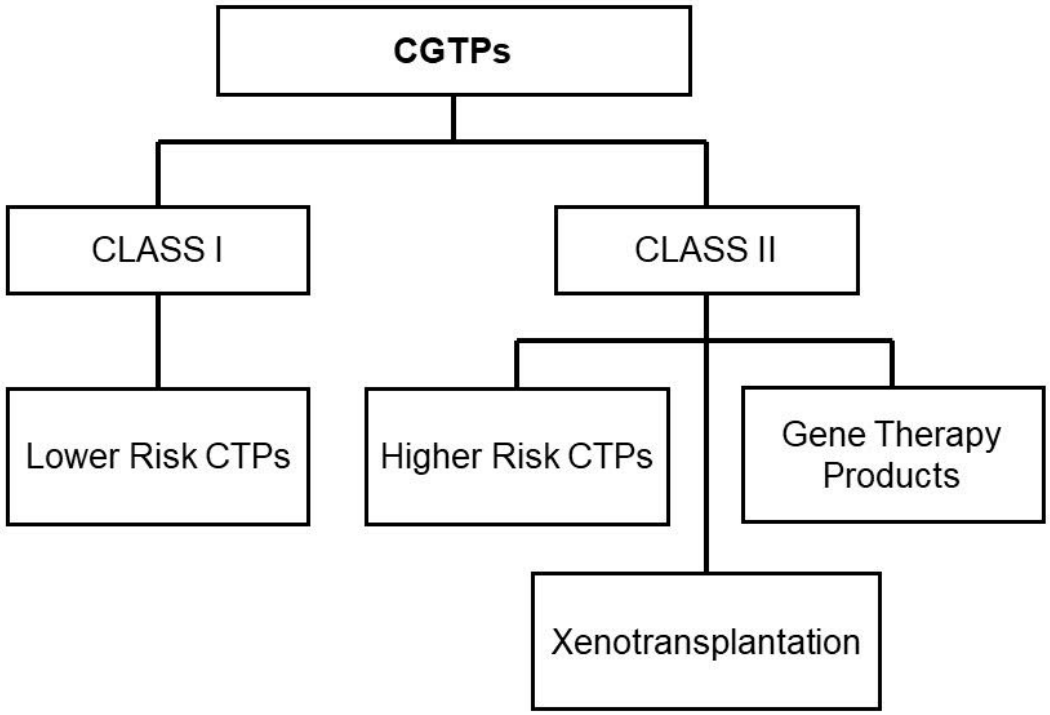
For examples of structural tissue and cells or non-structural tissues, and examples of minimal/ more than minimal manipulations for each tissue type, please refer to *Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use*

In essence, for a cell/tissue to be considered as minimally manipulated, data will need to be provided to support that the manufactured tissue/cell fulfils the definition of minimal manipulation (as stated in the earlier part of this section).

6. RISK CLASSIFICATION OF CELL AND GENE THERAPY PRODUCTS (CGTPs)

The risk-based approach to CGTPs regulation means products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight. Thus, two classes/ categories of products have been identified.

Figure 1: Classification of Cell and Gene Therapy Products (CGTPs)



Class II cell and gene therapy products (CGTPs) regulated by the DCA are broadly divided into cell therapy, xenotransplantation, and gene therapy, means any product containing or consisting of:

a. **Cell therapy:** viable human cells or tissues
    i. that have been manipulated to change their biological characteristics; or
    ii. not intended to be used for the same essential functions in the body; or
    iii. combined with another drug/article/device; or
    iv. that have a systemic effect if intended for allogeneic use
b. **Xenotransplantation (refer Annex I):** viable animal cells or tissues
c. **Gene therapy (refer Annex II):** recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence it contains or to the product of gene expression of this sequence

Cellular therapeutics that incorporate gene repair or genetic modification must adhere to regulatory guidelines set forth for both cell therapy and gene therapy products.

6.1 CLASS I CGTPs: LOWER RISK CELL THERAPY PRODUCTS (CTPs)

For lower risk products, the regulatory framework focuses on minimising the risk of transmission of infectious diseases. A Class I CGTP is not regulated under the **Control of Drugs and Cosmetics Regulations 1984**. However, the private healthcare facilities and services (PHFS) are regulated through site or facility licensure by the Medical Practice Division under the Private Healthcare Facilities and Services Act 1998 (Act 586). The use of such products in clinical setting will be regulated under the Medical Development Divisions, Ministry of Health Malaysia.

The medical practitioners are regulated by the Malaysian Medical Council (MMC) according to the Medical Act 1971 [Act 50] while dental practitioners are regulated by the Malaysian Dental Council (MDC) according to the Dental Act 2018 [Act 804], respectively.

The manufacturer and practitioner are responsible for ensuring that the handling of cells/ tissue complies with Good Tissue Practice principles.

Class I CGTPs are products that meet all four of the following criteria:

a. It is minimally manipulated (not activated, encapsulated, expanded *ex vivo*, or genetically modified)
b. It is intended for **homologous use*** only, as determined by labelling/intended use and advertising
c. Its manufacture does not involve combination with another drug/article/device, except for water, crystalloids, or a sterilising, preserving, or storage agent (not raising new clinical safety concerns for the CTP)
d. It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or if it has such an effect, it is intended for autologous use

***Homologous use** means the replacement or supplementation of a recipient's cells or tissues with a CTP that performs the same basic function(s) in the recipient as the donor. A CTP is generally considered to be for homologous use when it is used to repair, construct, replace, or supplement:

a. Recipient cells or tissues that are identical (e.g. skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or

b. Recipient cells that may not be identical to the donor's cells, or recipient tissues that may not be identical to the donor's tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor.

This basically means cells or tissues are used clinically in a manner that is essentially the same as the natural endogenous function that it performed.

The document entitled *Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue Based Products: Minimal Manipulation and Homologous Use* may be referred.

6.2 CLASS II CGTPs: HIGHER RISK CELL THERAPY PRODUCTS (CTPs), GENE THERAPY PRODUCTS AND XENOTRANSPLANTATION

If a cell therapy product does not meet all the four criteria in Class I CGTP, then the product will fall under Class II CGTP. A Class II CGTP is "highly processed", used for other than normal function, is combined with non-tissue components, or is used for metabolic purposes". It is regulated as a biologic product. The evaluation for CTIL/CTX approval and product registration requires sufficient data demonstrating that the product is safe and effective in humans. Manufacturer is required to comply with GMP requirements. The product dossier should follow the ACTD format. Please refer to *NPRA's Drug Registration Guidance Document* for general information and requirements for registration of biologic products in Malaysia.

In the clinical development of a Class II CGTP, the quality and scientific evaluation must be adequate to permit an evaluation of the product's effectiveness and safety. Prior to clinical development phase, manufacturing description and pre-clinical pharmacology/ toxicology data must sufficiently characterise product quality and safety.

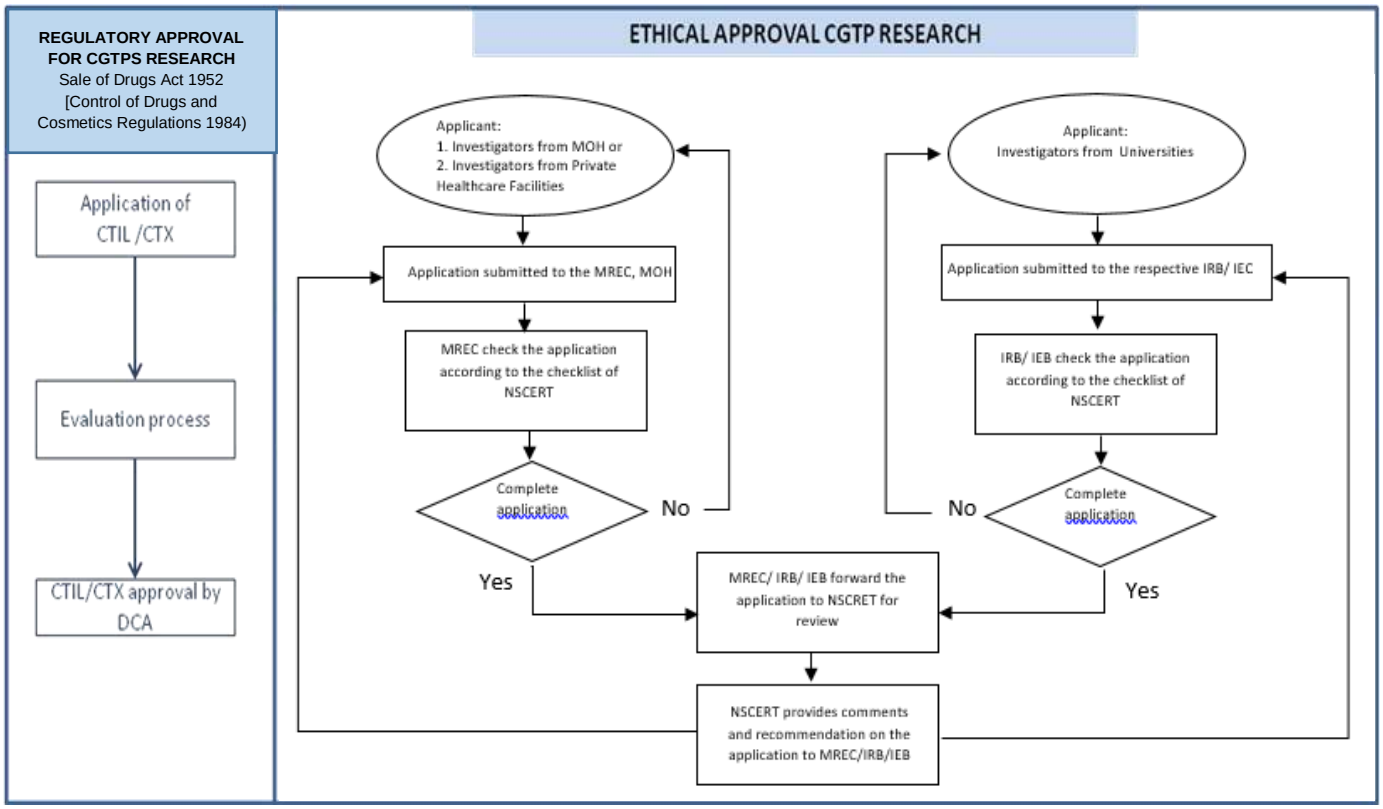
For a combination cell therapy product, proof must also be provided that the drugs and devices used having met the requirements of the relevant legislations. As currently envisioned – most, if not all, stem cell based therapies will be considered as product and would be subject to this framework.

6.3 MATRIX ON REGULATORY FRAMEWORK OF CELL AND GENE THERAPY PRODUCTS

To investigate the use of CGTPs in a local clinical trial, an application that reports data from pre-clinical studies on the likely safety and efficacy of the investigational product must be filed at NPRA. An approval for a Clinical Trial Import Licence (CTIL) or a Clinical Trial Exemption (CTX) is mandatory before a product is imported or manufactured for the purpose of clinical trial in Malaysia. For CTIL/CTX requirements, please refer to *Malaysian Guideline for Application of CTIL and CTX.* **Please refer also to *Checklist For Research on Stem Cell and Cell-Based Therapies* for further information on ethics approval.**

The following figures summarise the regulatory framework of CGTPs, and include information on relevant local authorities.

Figure 2: Clinical trial approval pathway for Class II CGTPs

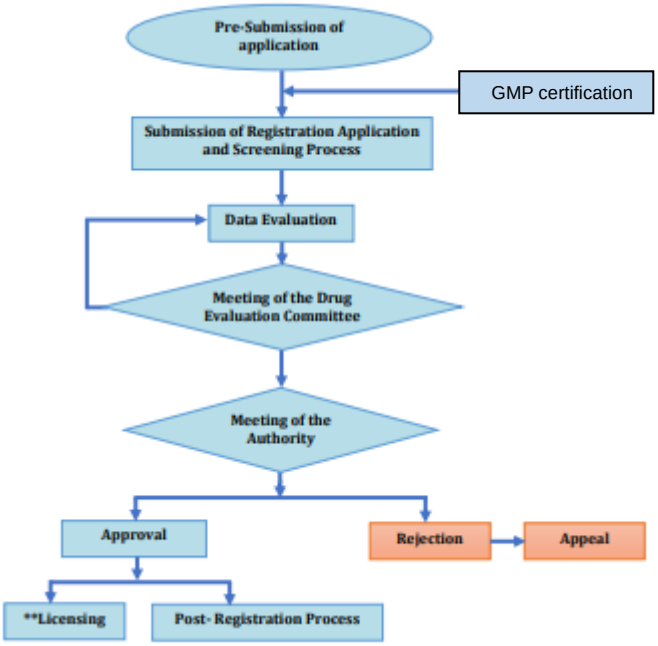


*** CTIL/ CTX shall only be issued once ethical and DCA approval has been obtained**

MREC = Medical Research and Ethics Committee
IRB = Institutional Review Board
IEC = Institutional Ethics Committee

NSCERT = National Stem Cell Research and Ethics Subcommittee

Figure 3. **Registration Process for Class II CGTPs**



** Good Manufacturing Practice (GMP) Certification*
*** Application for Manufacturer's, Import and/or Wholesaler's License*

7. QUALITY ASSURANCE FOR CGTPs

Cell based therapies are inherently challenging to Good Manufacturing Practice (GMP) compliance due to their human origin and associated problems in providing a mechanistic dose-related mode of action for their intended clinical use. The quality of a cell based product depends heavily on its manufacturing process. Therefore, standardised procedures to be followed strictly for all steps are absolutely necessary. The processing environment is a common source of microbiological contamination and should be controlled to minimise this risk and to prevent growth of contaminants. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of the biological product that may not be detectable in final product testing.

Therefore, the manufacture of CGTPs should be in compliance with the principles of Good Manufacturing Practices (GMP). The Pharmaceutical Inspection Convention/Scheme (PIC/S) GMP regulations comprise basic requirements applying to all products as well as annexes with detailed requirements for special types of products.

8. DATA REQUIREMENTS FOR REGULATORY SUBMISSION FOR CGTPs

As regards to the amount/ kind of data requirements for a CGTP application, the "one size fits all" approach cannot be applied. This is due to the wide spectrum of molecular complexity among the various products concerned. Although stem cells share the same principle characteristics of cell-renewal potential and differentiation, stem cell-based products are extremely diverse, i.e. do not constitute a homogenous class. Thus, the requirements to demonstrate safety and efficacy of CGTPs are essentially product class-specific or even product specific.

The data for submission are organised according to the ASEAN Common Technical Dossier (ACTD) format. Most CGTPs will require conduct of clinical trials prior to its marketing authorisation.

A risk-based approach will be taken in determining the extent of the quality, nonclinical and clinical data to be included in the dossier. The risk analysis should cover the whole development and risk factors considerations including:

a. The origin of the cells
b. Their ability to proliferate, differentiate or initiate an immune response
c. The level of cell manipulation
d. The combination of cells with bioactive molecules or structural materials
e. The level of integration of nucleic acid sequences or genes into the genome
f. Long term functionality
g. The risk of oncogenicity
h. The mode of administration or use
i. The nature of gene therapy product
j. The extent of replication competence of viruses or microorganisms used *in vivo*

The general requirements of a CGTP dossier are as shown in the following table:

Table 1: Registration requirements for Class II CGTPs

General	Requirements
Pre-Market Review/ Approval	Approval by DCA
Facility requirements	GMP evidence
Dossier requirements	Administrative Quality (CMC) Non-clinical Clinical RMP
Post marketing	Routine Pharmacovigilance Additional risk minimization activities such as patient registry

8.1 CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

It is imperative to develop appropriate pharmaceutical quality system for the entire "needle-to-needle" process from collection to transplant, including donation, procurement testing, coding, processing, preservation, storage and distribution of the cells.

All manufacturing steps need to be conducted in a controlled environment, to ensure the sterility of final product.

Sterility is a fundamental test requirement for cellular products. Since the product relies on the biological activity of living cells, none of the common sterilisation or virus elimination/ inactivation steps can be performed. In addition, tight specifications regarding freedom from adventitious agents in the source cells, all materials used in the process, as well as in the final bulk and end products need to be applied.

As biological processes may display inherent variability, quality risk management (QRM) principles are particularly important to develop a control strategy across all stages of manufacture to minimise variability and reduce contamination.

Also, sufficient information is required to assure the proper identification, safety, quality and purity of the cell product. In general, the GMP requirements for CGTPs are illustrated in the following table.

Table 2: Illustrative guide to manufacturing activities for CGTPs

Example products	Step of Processes involved			
Gene Therapy: mRNA	Linear DNA template preparation (1)	In vitro cell free transcription (3)	mRNA purification (3)	Formulation, filling (3)
Gene Therapy: in vivo viral vector	Plasmid manufacturing (1)	Establishment of MCB, WCB (3)	Vector manufacturing and purification (3)	Formulation, filling (3)
Gene therapy: in vivo nonviral vectors (naked DNA, lipoplexes, polyplexes, etc.)	Plasmid manufacturing (1)	Establishment of bacterial bank (3)	Fermentation and purification (3)	Formulation, filling (3)
Gene therapy: ex-vivo genetically modified cells	Donation, procurement and testing of starting tissue / cells (0)	Plasmid manufacturing (1) Vector manufacturing (2)	Ex-vivo genetic modification of cells (3)	Formulation, filling (3)
Somatic cell therapy	Donation, procurement and testing of starting tissue / cells (0)	Establishment of MCB, WCB or primary cell lot or cell pool (3)	Cell isolation, culture purification, combination with non-cellular components (3)	Formulation, combination, filling (3)
Tissue engineered products	Donation, procurement and testing of starting tissue / cells (0)	Initial processing, isolation and purification, establish MCB, WCB, primary cell lot or cell pool (3)	Cell isolation, culture, purification, combination with non-cellular components (3)	Formulation, combination, filling (3)

Note:

(0)	No GMP evidence required for the related manufacturer
(1)	Manufacturers involved in the manufacturing steps should be able to provide GMP evidence below: a. GMP certificate or GMP inspection report issued by: i. PIC/S Participating Authorities or; ii. World Health Organization (WHO) or; iii. Drug Regulatory Authority or b. Declaration from Qualified Person (QP) (for EU countries) or c. Self-declaration from competent person of related manufacturer or finished product manufacturer
(2)	Manufacturers involved in the manufacturing steps should be able to provide GMP evidence below: a. GMP certificate or GMP inspection report issued by: i. PIC/S Participating Authorities or; ii. World Health Organization (WHO) or; iii. Drug Regulatory Authority or b. Declaration from Qualified Person (QP) (for EU countries) or c. Accreditation evidence issued by (but not limited to): i. American Association of Blood Bank (AABB), ii. American Association of Tissue Bank (AATB), iii. Joint Accreditation Committee – International Society for Cellular Therapy & European Blood and Bone Marrow Transplantation (JACIE),

	iv. Foundation for the Accreditation of Cellular Therapy (FACT), v. The College of American Pathologists (CAP) vi. Evidence that premises is registered under UK Stem Cell Line Registry (https://www.ukri.org) (Note: Subject to further evaluation by NPRA)
(3)	Manufacturers involved in the manufacturing steps should be able to provide GMP evidence below: • GMP certificate or GMP inspection report issued by PIC/S Participating Authorities

**Remarks:*
Qualified person is the Authorized Person of the manufacturer or importer as described in the country's Marketing Authorization under the national law. The content of a declaration or batch certificate is recommended in PIC/S Annex 16 or as required under national law, or as required to facilitate arrangements between National Competent Authorities.

Once a cell or tissue product has been manufactured, a controlled process must be in place for review and release preferably before distribution of the product. However, a conditional release for shipping and transplant may be permitted where required to achieve desired clinical effect, as accompanied by additional controls that are in place based on detailed risk assessment, including for e.g. statistical analysis, trending information and in-process microbial contamination data.

The adage that quality cannot be tested into a product is particularly true for CGTPs. It is expected that as a product transitions from one developmental phase to the next (pre-clinical, clinical, licensure), the control of the manufacturing and testing process will become more stringent. Likewise, the release process will become more robust.

The following information should be included in the CMC section of a CGTP product dossier, to be organised in accordance with the ACTD – Part II format.

8.1.1 STARTING AND RAW MATERIALS

Starting materials shall mean all the materials from which the active substance is manufactured (e.g. donated cellular material) while raw materials are the reagents that are used during the manufacturing process but that are not part of the finished product (e.g. serums, digestion enzymes, growth factors, cytokines, antibiotics, resins, media etc).

As CGTPs are complex products, the source, origin and suitability of biological starting and raw materials should be clearly defined. The identification of all starting materials should be in compliance with the requirements appropriate to its stage of manufacture.

In all aspects of sourcing, banking and preparation of cell cultures, the principles of **Good Cell Culture Practice** should be observed, the fundamentals of which are summarised below:

a. All raw materials of human and animal origin must be stringently sourced and qualified based on product and process-related requirements and acceptance criteria
b. All raw materials derived from humans and animals must be assessed and tested based on risk of adventitious agent introduction (e.g. microbial contamination, other cell line contamination) in the manufacturing process of CGTPs
c. The authenticity, provenance and genotypic/phenotypic characteristics of the source cells must be demonstrated
d. The stability and functional integrity of the cells in extended *in vitro* passage must be monitored
e. Variation in physical culture parameters (e.g. pH, temperature, humidity, gas composition) which can significantly influence the performance and viability of cells and should be specified with established tolerances, and relevant equipment calibrated and monitored
f. Any culture reagents prepared in the laboratory should be documented, controlled for quality and released against an established specification
g. Care should be taken to minimise manipulations in the *in vitro* processing of cells to improve process consistency.

Qualification of source cells

The sources of donor cells:

a. Patient's own cells (autologous cell products)
b. Cells from another human being (allogeneic cell products)
c. Cells derived from animals (xenogeneic cell products)

Regardless of the source, the following principles generally apply:

a. The initial procurement of cell should always be conducted using aseptic techniques and universal precautions to minimise the risks of contamination, infection and pathogen transmission
b. The transport of human tissues and cells to the manufacturing site must be controlled, with documentary evidence of adherence to the specified storage and transport conditions at the manufacturing site

c. For products where production batches are frequently small, the risk of cross-contamination where cell preparations from different donors with various health statuses should be controlled under defined procedures and requirements
d. The risk of infectious disease transmission from starting materials to the product recipient during their passage along the supply chain must be assessed, with particular emphasis on TSE, mycoplasma, endotoxin, donor specific viruses, and appropriate microbiological screening profile based on the country of donor origin

Please refer *Requirements for Registration of Blood Products in Appendix 4: Drug Registration Guidance Document* for relevant checklists to be filled.

- The pharmaceutical quality system must allow all raw materials including tissues and cells to be traced from donor to recipient, and vice versa.

Donor Screening and Testing

The safety of the donor and patients need to be ensured through proper screening and testing. This is to avoid disease transmission and to safeguard both the donors and patients. For requirements on donor screening and testing, please refer to the guidelines published by relevant authorities such as:

a. National Standards For Stem Cell Transplantation
b. National standards For Cord Blood Banking And Transplantation
c. Transfusion Practice Guidelines

In the case of an allogeneic donor, these additional principles apply:

a. Medical history and health status of the donor should be investigated for potential further risks to the recipient
b. The importance of matching for histocompatibility antigens (HLA Class I and/or II and perhaps minor antigens in some cases) between donor and recipient should be addressed and typing procedures and acceptance criteria to be provided
c. As characterisation of multiple donor mixtures may be challenging, the establishment of a single master cell source may mitigate variability. Nevertheless, all cell lots must be appropriately characterised.

Isolation of Cells from Organ/Tissue

The procedure to obtain the cells from the organ/tissue must be described (with respect to the type of enzyme, media, etc.). A procedure performed repeatedly must be validated. Considerations should be given to the degree of disruption

applied to the tissue in order to preserve its functional integrity and to minimise cell-derived impurities (e.g. cell debris, cross contamination with other cell types) in the product. All isolation steps should be documented, with risk assessments and controls implemented.

Cells cultured in or on a matrix/device/scaffold

If cells are grown directly inside or on a matrix/device/scaffold, the quality of the combination product relies predominantly on properly controlled manufacturing process. For such products, the cell culture process has to be thoroughly validated with the effect of the device on the cell growth, function and integrity taken into account. In addition, the effect that the cells may exert on the device (e.g. on rate of degradation) need to be considered.

Raw materials, excipients and adjuvants

All raw materials, excipients and adjuvants must be qualified, i.e. characterisation of identity, purity, functionality, and demonstration of freedom from adventitious agents and suitability.

Other materials and reagents

Other materials and reagents to which the product is exposed to during manufacturing should be clearly specified and evaluated for its suitability of use. All materials and reagents should be sterile, unless otherwise justified. It is recommended to keep the use of such materials to a minimum and to avoid the use of reagents with sensitisation potential e.g. β-lactam antibiotics.

Transmissible Spongiform Encephalopathies (TSEs)

As with other biologics, the use of animal-derived material is unavoidable for production of some CGTPs. Therefore, measures taken to minimise the risk of TSEs need to be documented by filling in *Checklist A/B in Requirements for Registration of Blood Products in Appendix 4: Drug Registration Guidance Document.*

When manufacturers have a choice, the use of materials from non TSE-relevant animal species is preferred. The rationale for using materials derived from TSE relevant animal species instead of materials from non-TSE relevant species or of non-animal origin should be given. If materials from TSE-relevant animal species have to be used, consideration should be given to all the necessary measures to minimise the risk of transmission of TSE.

Viral safety

For products manufactured using human or animal materials, the risk of viral contamination and transmission must be mitigated using these complementary measures, as described in the *ICH Q5A: Viral safety evaluation of biotechnology product derived from cell lines of human or animal origin*:

a. Selection of source of materials and testing for viral contaminants
b. Testing the capacity of the production process to remove and/inactivate viruses
c. Testing of viral contamination at appropriate stages of production.

Where appropriate, one or more validated procedures for removal or inactivation of viruses should be applied.

8.1.2 CELL BANKING SYSTEM

The overall quality of the cell bank is a critical parameter that impacts the safety and efficacy of the final product. Sufficient knowledge of the properties of the original cell source is an important aspect of ensuring product quality. Generally, the establishment of a cell banking system should comply with the following principles:

a. The cell bank system used should be adequately described, including: origin and history of cells, procedures such as freezing and thawing, characterisations, testing for contaminating organisms, and stability monitoring for expiration dating
b. The number of passages between seed lot or cell bank, the active substance and the finished product should be consistent with specifications and across product batches. As part of product lifecycle management, the establishment of seed lots and cell banks should be performed under circumstances which are demonstrably appropriate in accordance to GMP requirements. Their on-going stability and suitability for use should be further demonstrated by trend evaluation and the consistency of the characteristics and quality of the successive batches of product.
c. Some specific elements to consider and document when developing an appropriate panel of tests to assess cell bank safety include: source material from which the bank is derived, cell line history, procedures used to establish the cell bank, materials and reagents used during manufacture, critical cell intermediate, final product characteristics, microbiological testing for bacteria/fungus/mycoplasma/virus, and expiration dating.
d. Generally, the panel of tests is more extensive for the MCB than the WCB. At the very minimum, the cell bank should be tested for identity (phenotypic

characterisation, genotypic marker, isoenzyme testing), purity, viability, stability, oncogenicity, tumorigenicity, and safety (sterility, free from contaminating agents including adventitious agents, exo/ endogenic viruses, mycoplasma).

e. If the need arises to introduce genetic materials into the cells, the expression construct has to be described and characterised, including: origin, identification, isolation and sequence. The cell banks as well as the final product have to be tested for gene expression, integrity, copy numbers and stability of the inserts.

In the clinical development stage of a CGTP, the MCB or WCB possibly becomes the source of cells for every batch produced for human trials. In this case, appropriately tested and qualified primary cells may be used in lieu of creation of cell banks.

Further guidance on cell banking and characterisation can be obtained from the following documents:

a. ICH Q5A: Viral safety evaluation of biotechnological products derived from cell lines of human or animal origin
b. ICH Q5D: Derivation and characterisation of cell substrates used for production of biotechnological/biological products
c. Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterisation of cell banks, Annex 3: WHO TRS 978, 61st Report

8.1.3 CHARACTERISATION

The characterisation of a CGTP should encompass all the components present in the finished product, including matrices, scaffolds and devices. An extensive characterisation of the cellular component should be established in terms of identity, purity, potency and suitability for the intended use, unless justified. When considering the extent of characterisation, the following issues should be taken into account: (i) autologous cells vs. allogeneic cells (ii) extensively or minimally manipulated *in vitro* (iii) immunologically active or neutral (iv) proliferative capacity of the cells (v) cell-like or tissue-like organisation and dynamic interactions amongst cells and with the structural component; and (vi) intended use.

The characterisation should be designed to allow setting up the routine controls that will be applied for release of the active substance and finished product as well as those to be performed at several steps of the process to guarantee batch consistency. If biologically active molecules are present as components of the cell

based products, these have to be described fully and their interaction with the other components of the product and the surrounding tissues after administration should be characterised. In the course of product development, it is imperative to validate surrogate markers of the identity and potency of cell products. This should involve an appropriate range of *in vitro* and where necessary *in vivo* methods. For an extensive guidance on CGTP characterisation, please refer to *EMA Guideline on human cell-based medicinal products***.**

8.1.4 MANUFACTURING PROCESS

The variety of distinct cell types, tissue sources, and modes of manufacture and use necessitate individualised approaches to cell processing and manufacture. The success of a CGTP highly depends on the robustness of its manufacturing process. Quality must be built into the product, rather than achieved by testing during batch release. Since the quality of CGTPs is determined by the production process, the use of standardised procedures and ensuring high quality documentation for all steps of production from sourcing to final product are absolute prerequisites.

The manufacture of CGTPs should be carefully designed and validated to ensure product consistency. The consistency specifications should be defined and justified.

The manufacturing area should be physically separated from the area where biological fluids, tissues or organs are collected. If diverse tissues and cellular products are collected, processed and stored in the same manufacturing area there is an increased risk of cross contamination during each step of the procedure, e.g. via processing equipment or in storage containers such as liquid nitrogen tanks, and therefore, adequate control measures to prevent cross contamination should be put in place.

The manufacturing processes of CGTPs require a number of operations and manipulations by individuals who are well trained in aseptic processing techniques. Equipment and premises used for manufacturing should be suitable and qualified for aseptic production. It is recommended that dedicated, product-specific or single-use equipment are used in the production, whenever possible. If the same equipment is used for production of e.g. multiple autologous products, sanitation and sterilisation procedures should be described and validated.

A detailed description of the manufacture of the active substance and of the finished product should be provided. The type of manipulation(s) required for cell processing and the physiological function of the cells shall be described. A flow diagram of the entire process starting from biological fluid/tissue/organ or from cell banks should

be prepared indicating critical steps and intermediate products (e.g. intermediate cell batches), as well as operating parameters, in-process controls and acceptance criteria. Manufacture of combination products consisting of cells and matrices/ devices/ scaffolds, require additional consideration regarding the cell-matrix/ scaffold interactions and quality issues raised there from. Attention should be paid on biodegradable materials which may possess the potential for environmental changes (e.g. raising pH) for the cells during the manufacture or after administration.

Where possible, components of animal origin used in the culture or preservation of cells should be replaced with human components or with chemically defined components to reduce the risk of accidental transfer to patients of unwanted chemical or biological material or pathogens.

Information on procedures used to transport material during the manufacturing process of the product, including transportation, storage conditions and holding times, should be provided.

For the purpose of consistency and traceability, batch definition, i.e. a clear definition of a production batch from cell sourcing to labelling of final container should be provided (i.e. size, number of cell passages, pooling strategies, batch numbering system). In the autologous setting, the manufactured product should be viewed as a batch on its own.

8.1.5 MANUFACTURING PROCESS VALIDATION

As with all biological processes, manufacturing should be designed with validation in mind. The entire manufacturing process, including cell harvesting, cell manipulation processes, maximum number of cell passages, combination with other components of the product, filling, packaging, transport, storage etc., should be validated. Validation of the production process of a combination product should encompass all steps from separate components up to the final combination to ensure consistent production.

It should be demonstrated that each step of the manufacturing process of the active substance, supportive components and final product is well controlled. The selection and acceptance criteria of the operational parameters and the in-process controls should be justified. Putative variability, related to starting materials and biological processes, should be taken into account in the validation. Furthermore, the critical points of the manufacturing process should be defined and validated, especially the aseptic processing.

Any preservation steps, holding periods and/ or transportations of the active substance, final product, supportive structures or intermediate products during the manufacturing process should be validated.

In case of limited sample sizes (e.g. autologous preparation for a single administration), it is recommended that a more extensive validation is performed with cell preparations of comparable characteristics but available in sufficient amounts for validation purposes. It is recommended that validation of such a manufacturing process is performed (depending on the product characteristics) for adventitious agents, identity, potency, viability, purity and other product-specific parameters.

8.1.6 QUALITY CONTROL

Specific tests and quality control (QC) paradigms are required for implementing in-process and product lot release for CGTPs. An array of unique QC tests is used for stem cells products: e.g. tests to determine extent of differentiation using gene expression, evaluation of cell morphology, etc.

Analytical methods

The complexity and scope of cell based therapies are reflected in the wide range of analytical methods that are used to establish in-process controls and final product release criteria. Quality specifications for CGTPs should be chosen to confirm the product's quality, safety and potency.

The development and setting of specifications for cell and tissue products should follow the principles outlined in *ICH Q6B: Specifications: Test procedures and acceptance criteria for biotechnological/biological products*. All release testing should be performed using methods validated at the latest at the time of submission of an application. Please refer to *ICH Q2(R2) Validation of analytical procedures*.

The following table provides some basic analytical tests for CGTPs.

Table 3: Examples of Analytical Tests for Cell and Gene Therapy Products

Test	Cell Therapy Products	Gene Therapy Products	
		Viral	**Non-viral and Antisense Oligonucleotide***
Identity of biological substance	i. Surface marker determination ii. Species iii. Morphology iv. Genotypic/phenotypic markers v. Bioassay vi. Biochemical marker	i. Plasmid mapping ii. PCR iii. Immunoassay for expressed gene iv. Sequencing	i. Restriction enzyme map ii. PCR iii. Immunoassay for expressed gene iv. Sequencing
Dose	i. Viable cell number ii. Enumeration of specific cell population iii. Total DNA iv. Total protein	i. Particle number ii. Transducing units iii. Total protein iv. HPLC	i. Plasmid-DNA weight ii. HPLC iii. Capillary electrophoresis
Potency	i. Viable cell number (cells intended for structural repair) ii. Bioassays: - Colony-formation assay - Function of expressed gene - Induction of secondary effect (e.g., human leukocyte antigen (HLA) induction, secretion of cytokines, and upregulation of surface marker) iii. Telomere assessment (length, integrity etc)	i. Function of expressed gene (induction of secondary effect and other bioassays)	i. Function of expressed gene (induction of secondary effect and other bioassays)

Test	Cell Therapy Products	Gene Therapy Products	
		Viral	**Non-viral and Antisense Oligonucleotide***
Purity	i. Percentage of viable cells ii. Percentage of transduced/transfected cells iii. Percentage of cells with specific surface marker iv. Process contaminants (e.g., serum)	i. Residual host-cell DNA ii. Process contaminants (e.g., serum and cesium chloride) iii. Residual helper virus iv. Optical density ratio v. Residual host-cell proteins vi. Viral protein profile (HPLC assay for defective or immature particles) vii. Residual RNA	• Percentage of specific physical form (e.g., percentage supercoiled) • Residual host-cell DNA i. Residual RNA ii. Residual host-cell proteins iii. Residual solvents iv. Optical density ratio v. Process contaminants (e.g., cesium chloride)
Safety	i. Mycoplasma ii. Sterility iii. Pyrogen and endotoxins iv. Adventitious viruses v. Residual virus vi. Replication competent vector virus, RCV	i. Sterility ii. Pyrogen and endotoxins iii. Adventitious viruses iv. RCV	i. Mycoplasma ii. Sterility iii. Pyrogen and endotoxins

Table adapted from the United States Pharmacopeia, USP 43-NF38

HPLC = high performance liquid chromatography

RCV = respiratory syncytial virus

*Antisense Oligonucleotide: only applicable if not chemically synthesized (e.g. cell-based or viral vector-mediated synthesis)

In-process controls

In-process control tests enable manufacturer to gather process and product characterisation data, useful in assessing the impact of process changes or

excursions. Cells in culture age may accumulate both genetic and epigenetic changes, as well as changes in behaviour. Unfortunately, scientific understanding of genomic stability during cell culture is primitive at best and assays of genetic and epigenetic status of cultured cells are still evolving. Defining optimal quality control for cultured cell products remains a key goal.

Examples of in-process controls:

a. Enumeration and viability
b. Expression of phenotypic or genotypic markers
c. Verification of morphology against visual reference standards
d. Determination of population doublings, passage number, age of culture
e. Assays of product- and process-related impurities
f. Monitoring of culture system parameters (e.g. % relative humidity, pH, glucose, etc.)
g. Functional tests such as colony forming units (CFU) and expression of cell specific proteins
h. Microbiological (sterility, endotoxin, mycoplasma) contaminants should be tested periodically in cells or spent media to ensure that aseptic conditions are maintained throughout processing.

Quality control of active substance/ final product

The release specifications of the active substance and finished product should be selected on the basis of parameters defined during the characterisation studies (see Section 8.1.3 CHARACTERISATION). Selection of tests is product-specific and has to be defined by the manufacturer.

If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process tests, this needs to be justified. In these cases, an adequate quality control has to rise from the manufacturing process, supported by the results of the clinical studies. These exceptions may include the following:

a. Some release tests might not be feasible on the combined components of the active substance/ finished product for technical reasons
b. A complete release testing cannot be finalised before the product is administered to the recipient due to time restrictions. However, a critical set of essential tests that can be performed in the limited time prior to clinical use must be defined and justified. Whenever feasible, retention samples should be stored for future analysis. Integration of specialised test methods

within a manufacturing facility can be of particular value for stem cell products with short shelf lives.

c. Sometimes, rapid microbiological methods (RMM) are used. Alternatively, the United States Pharmacopeia (USP) and the European Pharmacopeia (EP) have recently published relevant chapters as follows:
    - USP <1223> Validation of Alternative Microbiological Methods
    - USP <1071> Rapid Microbial Tests for Release of Sterile Short-Life Products: A Risk-Based Approach
    - Ph. Eur. 5.1.6 Alternative Methods for Control of Microbiological Quality
    - Ph. Eur. 2.6.27 Microbiological Examination of Cell-Based Preparations
d. The amount of available product is limited to the clinically necessary dose (e.g. due to very limited cell numbers at collection or low proliferation rates). The release of the product should be justified by the validation of the cell manipulation process and the in-process controls.

Product release testing

All CGTPs will undergo some form of release testing prior to issuance for clinical use. Product release is often handled through a Certificate of Analysis (CoA) system. The CoA summarises the characteristics of the product and the tests performed. Specifications for release testing should include identity, purity, dose, potency and safety evaluation.

8.1.7 STABILITY

A well-designed and executed stability program provides a high degree of assurance that the product is stable during its specified shelf life. Where feasible, stability testing should be carried out in accordance with the principles described in *ICH Q5C: Stability testing of biotechnological/biological products.*

Due to the complex nature of the active substance of CGTPs, requirement for stability should be defined on a case-by-case basis. Whenever possible, stability should be assessed for both the cellular as well as the non-cellular component prior to combination and together as a finished product in the final packaging.

It is very likely that for an industrial process providing off-the-shelf products, cells will have to be cryopreserved to maintain stability. If relevant, appropriate methods for freezing and thawing should be documented. The stability of the cells during

cryopreservation has to be tested. Viability is often assessed immediately post-thaw by simple live/dead assays that may not indicate true, long-term viability of the cells due to the phenomenon of preservation induced, delayed onset of cell death. The properties of thawed cells relating to viability, identity and quantitative function should be explored.

A valid in-use shelf life (after opening from the transport container) should be assigned to the CGTP. This should be supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity. All storage conditions including temperature range should be determined and supported by experimental data with regard to the maintenance of cell integrity and product stability during the defined period of validity.

Additional studies (e.g. cell adhesion studies, growth studies) may be necessary to demonstrate aspects of biocompatibility specific to cell based applications.

8.1.8 CONTAINER CLOSURE SYSTEM

A description of the container closure system should be provided. The choice of packaging materials should be addressed as part of the development pharmaceutics. Additional data may be required if packaging components are used in the transport and/or application procedure.

Compatibility with the product should be demonstrated. Leachables and extractables from product-contact packaging materials should be quantified, and limits should be established during product development. It should be indicated if the container closure *per se* has an approval from the Medical Device Authority (if the container serves a medical device function). Information on the sterilisation procedures of the container and the closure should be provided.

8.1.9 PRODUCT TRACEABILITY

A system allowing complete traceability of the product from the donor to the finished product is essential to monitor the safety and quality of CGTPs. The registration dossier should include a description of the traceability system, including coding and labeling strategies, to ensure tracking throughout the manufacturing process. Manufacturers should establish their coding systems in a rational way, building upon the coding system of the tissue establishment to enable the tracing from the donation to the final product. Barcoding and peel-off labelling systems may be suitable for product tracking. In addition to product traceability, full traceability from the donor to the recipient should be ensured.

8.1.10 COMPARABILITY CONSIDERATIONS

Changes in the process such as equipment changes, raw materials, starting materials, processes, manufacturing sites are common and frequent especially in the early stages of development.

The criticality of the changes and estimation of impact on the product should determine the amount of comparability data needed. Comparability study becomes a tool to demonstrate that the quality, safety and efficacy are not affected after the changes were introduced.

The following are references from EMA/US FDA that can be referred:

a. Questions and answers on comparability considerations for advanced therapy medicinal products (ATMP) (EMA)
b. Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA)
c. Reflection paper on design modifications of gene therapy medicinal products during development (EMA)
d. Draft Guidance for Industry: Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products (US FDA)

8.1.11 SUMMARY ON CMC DATA REQUIREMENTS

Table 4: Data to be included in the Quality Documentation of a Cell and Gene Therapy Product (CGTP)

For the quality documentation accompanying applications for marketing authorisation of a CGTP, special attention should be given (but are not limited) to the following items:

a) Information related to the starting and raw materials

- Type of cell and culture concerned (tissues, organs or biological fluids from which cells are derived)
  - Autologous or allogeneic
  - Geographical origin
  - Type of manipulation
  - Physiological function of the cells
- Description of source organs/tissues
  - Age, sex, microbiological status, exclusion criteria and country of origin
  - Site, type, operating process, pooling, transportation, storage and traceability as well as controls carried out on sampling
- Viral safety evaluation & other adventitious agents

b) Cell bank system

- Relevant requirements as to manufacturing and control of cell bank

c) Characterisation
(define critical product attributes, define and monitor/ control all cell types in the product, establish proper specifications)

- Identity (species of origin, banding cytogenetics, morphological analysis)
- Purity (adventitious microbial agents and cellular contaminants)
- Potency (defined biological activity)
- Suitability (karyology and tumorigenicity tests) for the intended medicinal use

d) Information on the manufacturing process and process validation

e) Information on quality control (in-process, drug substance and drug product)

f) Stability

g) Container Closure system

h) Product Traceability: Traceability of the product from the donor to the finished product

i) Comparability Studies

8.2 PRE-CLINICAL STUDIES

The objectives of the pre-clinical studies are to demonstrate proof-of-concept, define the pharmacological and toxicological effects predictive of the human response, not only prior to initiation of clinical trials, but also throughout clinical development.

However, traditional, standardised approaches to preclinical testing may not be appropriate for CGTPs. In addition, the diversity and complexity of CGTPs call for individualised pre-clinical testing programmes. Some specific considerations pertaining to CGTPs are as follows:

Proof-of-concept (POC)

a. The desired outcomes in the pre-clinical POC studies include identification of (i) a pharmacologically active effective dose range and dosing regimen (ii) an optimal route of administration; and (iii) a viable window for product administration relative to the onset of disease/injury
b. Information on the mechanism of action should be provided as detailed as possible to facilitate an informed development of a potency assay with potential biomarkers for activity and toxicity for clinical monitoring.
c. The chosen animal model should reproduce the disease or condition of the patients as close as possible with ideally similar pathophysiology as in patients. Appropriate animal models may include naturally occurring spontaneous or experimentally induced disease models, transgenic knock-out or knock-in disease models, as well as specifically humanised animal models
d. If relevant animal models cannot be developed, in vitro studies may replace animal studies. The rationale underpinning the non-clinical development and the criteria used to choose a specific animal model must be justified. Expression level of biologically active molecules, the route of administration and the dosages tested should reflect the intended clinical use in humans

Cell kinetic & Biodistribution

a. The fate of infused cells and tissue distribution profile need to be determined.
b. Conventional ADME studies are usually not relevant for human cell based product. Pharmacokinetics for CGTPs depend on the type of the CGTP and include biodistribution (distribution and migration), as well as elimination parameters (persistence and clearance).
c. The need for biodistribution studies is dependent on the administration route as well as the structural or physiological containment of the cells eg. local, systemic or contain within a scaffold etc.

d. Biodistribution data should be available to provide information on the persistence, duration of effect, and migration to target and non-target organs in order to support the design and duration of safety study(ies).

Pre-clinical safety studies

a. A critical step in the translational process is a thorough pre-clinical assessment of product safety, including local and systemic toxicities, dose-toxicity response, and onset and reversibility of any toxicity findings. In addition, the feasibility and safety of the delivery device and procedure need to be sufficiently evaluated.
b. The use of multiple species (small and large animals – depending on aim of study) or animal models may be necessary to adequately model the functional aspects and potential toxicities of the investigational CGTP. The need for animal models is especially strong in the case of extensive manipulation of cells and/or when cells have been derived from pluripotent stem cells
c. A hybrid pharmacology-toxicology study in a model of disease/injury that more adequately reflect the clinical profile is recommended
d. The need for additional toxicity studies e.g. genotoxicity, tumourigenicity, reproductive and developmental toxicity, and immunotoxicity studies should be determined on a case by case basis taking into consideration the risks related to the nature and characteristics of the particular class of CGTPs and the intended clinical use. The mode and schedule of administration shall appropriately reflect the clinical dosing.
e. Cells grown in culture, particularly for long periods or under stressful conditions, may become aneuploid or have DNA rearrangements, deletions, and other genetic or epigenetic abnormalities that could predispose them to cause serious pathologies such as cancer. Risks for tumorigenicity in stem cell products must be assessed especially when extensively manipulated in culture or when genetically modified.
f. Uncontrolled proliferation of the administered cells and insertional mutagenesis following administration of integral viral vectors are risks unique to CGTPs. Thus, tumorigenicity and genotoxicity studies may be necessary.
g. The extent of non-clinical data for tumorigenicity is dependent on the perceived risk of tumour formation, and should be based primarily on in vitro and ex vivo analyses which in some cases may need to be supplemented with in vivo data. Tumorigenesis studies should preferably be performed with cells that are at the limit of routine cell culturing or even beyond that limit.
h. Genotoxicity studies are not considered necessary for human cell based product, unless the nature of any expressed product indicates an interaction directly with DNA or other chromosomal material. The requirement for genotoxicity studies of gene therapy product involving host-DNA integration will depend on the way the final product will be delivered (local versus

systemic), to which tissue/organ the gene therapy product will be targeted and the biological status of the cells to be targeted.

i. Safety pharmacology data are not routinely needed for CGTPs. When potential effects on major vital physiological functions i.e. cardiovascular, central nervous system, or respiratory function are anticipated, appropriate safety pharmacology data should be available before human exposure. Safety pharmacology endpoints can be incorporated in the toxicity studies, if feasible.
j. The need for reproductive studies is dependent on the CGTP and should be considered on a case-by-case basis.
k. Repeated dose toxicity studies are only relevant if the clinical use includes multiple dosing.
l. The induction of an immune response against the cells themselves and/or towards cell-derived pharmacological active substances might modulate the efficacy of the CGTP. Therefore, the possible immunogenicity of a CGTP should be considered in the selection of appropriate animal models and as part of the overall toxicology assessment of the product including e.g. histological analysis of immune system activation both locally and systemically. The impact of an unwanted immune response on the fate of an administered CGTP needs to be addressed.
m. Cell cultures and animal models should be used to test the interaction of cells with drugs (e.g. immunosuppressants and drugs to treat underlying disease process) to which recipients will be exposed.

Combined CGTPs

a. For products intended to provide some mechanical support, biomechanical performance should be comprehensively assessed at multiple time points following product administration.
b. In addition, the safety and suitability of all structural components for their intended function must be demonstrated, taking into account their physical, mechanical, chemical and biological properties.

Good Laboratory Practice (GLP)

It is generally expected that pivotal pre-clinical safety studies are carried out in conformity with the principles of OECD GLP. However, it is recognised that, due to the specific characteristics of CGTPs, it would not always be possible to conduct these studies in full conformity with GLP. For example, when certain technical expertise, unique animal care issues or endpoints may not be available at a GLP testing facility. If a pivotal pre-clinical safety study has not been conducted in conformity with the GLP principles, a proper justification should be submitted. This justification should also address the potential impact of the non-compliance on the reliability of the safety data.

Directive Bil 9/2016: https://www.npra.gov.my/index.php/en/circulars-directives/99-english/directive-general/1876-keperluan-good-laboratory-practice-glp-bagi-kajian-keselamatan-bukan-klinikal-untuk-tujuan-pendaftaran-produk-new-chemical-entity-nce-biologik-dan-produk-herba-dengan-tuntutan-terapeutik-tinggi-2.html

Responsible animal research should adhere to the principles of the three R's – Reduce numbers, Refine protocols, and Replace animals with *in vitro* or non-animal platforms wherever possible. Further, animal models may not replicate the full range of human toxicities. Therefore, particular vigilance must be applied in pre-clinical analysis of the toxicities of cell based interventions. In any case, comparability of the product used in pre-clinical experiments to that intended to be used as clinical material should be ensured.

In conclusion, the extent of the non-clinical data package is determined on a case-by-case basis taking into consideration the risks, or the lack of risks, associated with the product and the intended clinical use, the availability of animal models and publicly available information from similar type of products.

For details on non-clinical studies, please refer to:

a. EMA Guideline on Human Cell-based medicinal products
b. EMA Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials
c. US FDA Preclinical Assessment of Investigational Cellular and Gene Therapy Products

8.3 CLINICAL STUDIES

General aspects

In general, when a CGTP enters the clinical development phase, the same requirements as for other biologics apply. The necessity and extent of clinical studies will be considered on a product-specific basis.

The clinical development plan should be designed in accordance to the existing general guidance's and specific guidance's for the condition evaluated. Due to the diverse biology and scientific issues associated with CGTPs, it is important to conduct a careful risk-benefit analysis, performed in the context of the particular clinical indication under study.

Any deviation from Phase I to Phase III clinical trials progression needs to be justified by the specificity of the CGTP, the pre-clinical studies, previous clinical experience and the treated pathology.

The clinical development programme should incorporate the following points of concern in the trial design:

a. CGTPs may require surgery or other invasive procedures for delivery to the target site. A concomitant treatment may also be required to obtain the intended therapeutic effect. The biological effects of CGTPs are highly dependent on the *in vivo* environment, and may be influenced by the replacement process or the immune reaction either from the patient or from the cell-based product. These requirements coming from the clinical development should be taken into account for the final use of these products. Their standardisation and optimisation should be an integral part of the clinical development studies. The therapeutic procedure as a whole, including the method of administration and required concomitant medication such as immunosuppressive regimens needs to be investigated and described in the product information.
b. Some CGTPs can persist in humans for an extended period after a single administration, or have an extended duration of effect even after the product itself is no longer present. The effects of the product might evolve over time (e.g., stem cells that proliferate and differentiate to form tumours). Therefore, evaluation of safety might require observation of subjects for a substantial period of time to understand the safety profile.
c. CGTPs have the potential to elicit an immune response in the recipient's body. Immunogenicity may be significant in one of the two following ways. First, pre-existing antibodies, or antibodies that develop after administration of the product, could reduce or extinguish a beneficial effect, cause an adverse reaction (e.g., an autoimmune syndrome), or influence safety or

efficacy if there are any subsequent administrations. Second, in patients who have a condition that could be treated with a cellular, tissue, or organ transplant in the future, the development of antibodies to an allogeneic CGTP might jeopardise the prospect for successful transplantation.

Early phase trials

The pre-clinical data generated may not always be as informative as other pharmaceuticals since it is usually not feasible to conduct traditional PK/PD studies. Due to various issues, such as species specificity and immunogenicity, extrapolation from a CGTP dose administered in animals to a clinical dose can be less reliable than the customary allometric scaling typically used for pharmaceuticals. These issues can limit the ability of the pre-clinical data to guide various aspects of the design of the early phase clinical trial.

Thus, the design of early-phase clinical trials of CGTPs often involves consideration of clinical safety issues, pre-clinical issues, and CMC issues that are encountered less commonly or not at all in the development of other pharmaceuticals. For CGTPs, these early phase trials often assess not only safety of specific dose levels, but also other issues, such as feasibility of administration and pharmacologic activity.

CGTPs sometimes require specialised devices or novel procedures for administration, customised preparation of products, special handling of products (e.g., very short expiration time), or adjunctive therapy. In these cases, sponsors should consider designing early phase trials to identify and characterise any technical or logistic issues with manufacturing and administering the product.

A common secondary objective of early phase trials is to obtain preliminary assessments of product activity, using either short-term responses or longer-term outcomes that could suggest potential for efficacy. For CGTPs, these outcomes might include specialised measures such as gene expression, cell engraftment, or morphologic alterations, as well as more common measures such as changes in immune function, tumour shrinkage, or physiologic responses of various types.

Product development rationale

The information presented in this section should address the following:

a. Compare product to current treatment options
b. Rationale for product development as an unmet medical need
c. Important questions to clarify in clinical trials
d. Most suitable cell types
e. Optimal timing/dose/delivery/site
f. Survival/distribution/engraftment/integration of CGTPs

g. (Ideal) mechanism that CGTP promotes recovery/structural reorganisation, e.g.: (i) secretion of growth factors (ii) cell-to-cell interactions
h. Association of inflammation/injury response to implant procedure
i. Potential adverse events

In addition, the applicant should attempt the following unresolved questions:

a. Long-term fate of transplanted cells in the recipient tissue
b. Ability of transplanted cells to find their optimum 'niche'
c. Potency of cells to transdifferentiate
d. Optimal angiogenic milieu needed for transplanted cells in hypoperfused tissue
e. Capability of recipient tissue to enable an enhanced environment to offer optimum, milieu-dependent differentiation of engrafted cells
f. Specific detection of engrafted cells/cell populations by labelling techniques
g. Optimal time course of availability and application for SC replacement therapy
h. Arrhythmogenic potential of implanted myocardial cells
i. Specific characterisation of the progenitor cells that should be measured to predict therapeutic effect of transplanted cells
j. Development of safe and reproducible catheter-based delivery systems for depositing SCs to recipient muscle/organ

In this section, a provision to refer to findings of previous studies (e.g. published literature, clinical practice guidelines, abstracts from conference – stratified by levels of evidence) can be considered.

Pharmacodynamics / Biodynamics

There is a relative lack of clinical experience with some CGTPs and the risk-benefit assessment will be especially difficult. Even if the mechanism of action is not understood in detail, the main effects of the product should be known.

When the purpose of the product is to correct the function of deficient or destroyed tissue, then functional tests should be implemented. If the intended use of the product is to restore/replace tissues, with an expected lifelong functionality, structural/ histological assays may be potential pharmacodynamic markers. Suitable pharmacodynamic markers, such as defined by microscopic, histological, imaging techniques or enzymatic activities, could be used.

When the product includes a non-cellular component, the combination should be assessed clinically for compatibility, degradation rate and functionality.

Pharmacokinetics / Biokinetics

Due to the unique nature of CGTPs, the conventional absorption, distribution, metabolism and elimination (ADME) studies are usually not relevant.

Methodologies to assess and monitor viability, proliferation/differentiation, body distribution/migration and functionality during the period of use of the product should be conducted.

If multiple administrations are proposed, the test schedule should address the expected *in vivo* life span of the product.

Dose finding studies

The selection of dose should be based on findings from quality determination, nonclinical development, and linked with the potency of the product.

For individualised dosage (e.g. cell mass density per body weight, volume of missing tissue, missing surface area), the dose to be tested should be supported by the evidence provided in earlier phases (Phase I/II) of studies.

It is generally recommended to quantify the Safe Maximal Dose (the maximal dose which could be administered on the basis of clinical safety studies without unacceptable adverse effects), taking into account the possibility of repeated administration. The dose of cells administered to humans should be below the minimum number of cells observed to form tumours in animal models.

Phase I/II studies should be conducted to identify Minimal Effective Dose (the lowest dose to obtain the intended effect) or an Optimal Dose Range (the largest dose range required to obtain the intended effect based on the clinical results for efficacy and tolerability).

Clinical efficacy

Clinical efficacy studies should demonstrate efficacy in the target patient population using clinically meaningful endpoints, to demonstrate an appropriate dose schedule that results in the optimal therapeutic effect, to evaluate the duration of therapeutic effect of the administered product and to allow a benefit-risk assessment taking into account the existing therapeutic alternatives for the target population. Confirmatory studies should be conducted in accordance to the existing general and specific guidelines for the condition being evaluated.

Deviations from established recommendations will need a justification. For example, the fact that the nature and the mechanism of action of the CGTP may be entirely novel does not mean necessarily that the therapeutic benefit should be measured by different endpoints from those recommended in the current disease specific guidelines (e.g. medicines vs. cell implants for Parkinson’s disease).

For new therapeutic applications of CGTPs where limited guidance exists, consultation with ethics committee and regulatory authorities on the clinical development plan, including the confirmatory studies, is highly recommended.

The use of previously validated or generally accepted surrogate endpoints is possible provided that a correlation-between clinical meaningfully endpoints and efficacy can be established. In the case where the desired clinical endpoint, such as prevention of arthrosis, can be observed only after a long follow up, the marketing authorisation can be based on surrogate markers. If the efficacy is dependent on the long-term persistence of the product, marketing authorisation may be granted with commitment by marketing authorisation holder to conduct long-term follow up / investigation plans post-marketing approval.

Clinical safety

The risks associated with CGTPs can be of a different nature from those typically associated with other pharmaceuticals. The main safety concern is to prevent transmissible diseases. The safety database should be able to detect common adverse events. The size of the database might be decided also in the light of previous clinical experience with similar products.

The risk of the therapeutic procedure as a whole, e.g. the required surgical procedures to administer the product or the use of immunosuppressive therapy, shall be evaluated and used to justify the clinical studies and the choice of the target patient population.

All safety issues arising from the pre-clinical development should be addressed, especially in the absence of an animal model of the treated disease or in the presence of physiologic differences limiting the predictive value of homologous animal model.

Particular attention should be paid to the biological processes including immune response, infections, malignant transformation and concomitant treatment during development and post-marketing phase.

For products with expected long term viability, patient follow-up is required in order to confirm long term efficacy and safety issue related to the product.

Clinical safety studies on repeated administrations should be performed as required by the risk analysis. The definition of Maximal Safe Dose should also take repeated administration into account.

Extensive patient monitoring and long term follow up

Extensive patient monitoring and long term follow up will be necessary to address the safety concerns and look for instances of release of endogenous viruses or clinical effects as a result of prolonged expression of foreign protein.

For pre-clinical development, besides the strong proof-of-concept, the focus should be on safety, especially tumourigenicity, cell persistence and trafficking *in vivo.* In this area, establishment of appropriate models, analytical methods and non-invasive imaging techniques will have to be developed.

The need for long term (maybe lifelong) follow up may interfere with the decision of the patient to withdraw from the trial. This has to be taken into consideration and addressed early in the clinical development programme. If possible, mechanisms with genetically induced potential to selectively kill the transplanted cells or use of devices for easy retrieval of cells in case of malfunction should be devised.

For details on clinical studies, please refer to:

a. EMA Guideline on Human Cell-based medicinal products
b. EMA Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials
c. US FDA Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products

8.4 LABELLING REQUIREMENTS FOR IMMEDIATE AND OUTER PACKAGING

In addition to labelling requirements of biologic products in the *Drug Registration Guidance Document (DRGD),* the following requirements apply:

a. The name of the product and, if appropriate, an indication of whether it is intended for babies, children or adults

b. The international non-proprietary name (INN) shall be included, or, if the product has no INN, the common name

c. A description of the active substance(s) expressed qualitatively and quantitatively including, where the product contains cells or tissues, the statement “This product contains cells of human/animal [*as appropriate*] origin” together with a short description of these cells or tissues and of their specific origin, including the species of animal in cases of non-human origin

d. The pharmaceutical form and, if applicable, the contents by weight, by volume or by number of doses of the product

e. A list of excipients, including preservative systems

f. The method of use, application, administration or implantation and, if necessary, the route of administration. If applicable, space shall be provided for the prescribed dose to be indicated

g. Any special warning necessary for the particular product

h. The manufacturing and expiry dates in clear terms (month and year; and day if applicable)

i. Special storage precautions (if required)

j. Specific precautions relating to the disposal of unused products or waste derived from products, where appropriate, as well as reference to any appropriate collection system in place

k. The manufacturer’s batch number and the unique donation and product codes

l. In the case of CGTPs for autologous use, the unique patient identifier and the statement “For autologous use only”

NOTE:
Some of the information required can also be included in the local package insert. Some information required can be exempted from the immediate label (refer to DRGD pertaining to labelling of small labels).

8.5. POST-REGISTRATION REQUIREMENTS

Adverse drug reaction reporting: Legal basis

a. In accordance with **Regulation 28: Reporting adverse reaction under Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952,** the product registration holders or any person who possesses any registered product shall inform immediately the Director of Pharmaceutical Services of any adverse reaction arising from the use of the registered product.

b. The adverse drug reaction reporting should be in accordance with the *Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders.*

Risk Management and Periodic Safety Update Reports

a. While CGTPs provide new possibilities for restoring, correcting or modifying physiological functions, or making a diagnosis, their novelty, complexity and technical specificity may bring along new, unexplored risks to public health and to individual patients. Thus, specific risk management requirements are called for. When preparing a risk management plan (RMP) for a particular CGTP, comprehensive scientific consideration should be given to the important identified or potential risks, and to the important missing information. The RMP is a dynamic, stand-alone document which should be updated throughout the lifecycle of the product.

b. Generally, routine pharmacovigilance and traceability of the CGTPs should be described in RMP and the product may need special long-term studies to monitor specific safety issues, including loss of efficacy.

c. Traceability in the donor-product-recipient axis, or product-recipient axis for autologous products, is required in all circumstances.

d. The long-term safety issues, such as infections, immunogenicity/immunosuppression and malignant transformation as well as the *in vivo* durability of the associated medical device/biomaterial component should be addressed in the RMP.

e. As many of the CGTPs incorporate living cells, the efficacy of these CGTPs is subject to their changing characteristics after their administration to patient over long periods of time. This may result in an increase (e.g. overexpression of a gene of interest) or decrease of efficacy, and the consequences for the patient may not be fully established during preregistration clinical trials.

f. The efficacy follow-up systems should use the same infrastructure for safety follow-up whenever feasible in order to ensure that safety and efficacy data are comparable and consistent. Safety follow-up alone might be appropriate for 'loss of efficacy' or 'less than expected efficacy' of CGTPs. However, further study of the product's efficacy profile in the post-authorisation phase may be considered on a case-to-case basis when it is inappropriate to use the safety follow-up alone for this purpose. For CGTP-specific concerns in the RMP, please refer *EMA Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products.*

g. A Malaysia-specific annex that highlight local safety concerns in the local population, local pharmacovigilance plan and local risk minimization activities planned to address the specific safety concerns should be submitted with the RMP.

h. Periodic safety update reports should discuss on-going cumulative efficacy and safety data as well as safety data relating to donors and close contacts. This should include assessment of the effectiveness of the risk management system and the results of any newly finished studies.

i. Product registration holders are required to monitor and report any product safety issues that arises locally or internationally to the NPRA and comply with all safety-related directives issued by the DCA. Please refer to the *Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders* for further information.

j. The Authority may also request for any additional information when there is a safety concern on a risk affecting the benefit-risk balance.

Patient Registry for Class II CGTPs

Safety signals can also be investigated through observational studies. For this purpose, the safety outcome of a CGTP can be tracked via a carefully designed non-randomised observatory trial. A relevant example of such a trial is a patient registry.

A registry may serve any or all of the following functions:

a. determination of effectiveness
b. surveillance on safety
c. evaluate access to and quality of healthcare

For regulatory expectations on the design and conduct of a registry, the *ICH Topic E2E: Pharmacovigilance Planning. Note for guidance on planning pharmacovigilance activities (ICH), Guideline on registry-based studies (EMA)* and the document entitled Guidance for Industry: *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment (US FDA)* may be referred and NPRA consulted.

ANNEX I. ADDITIONAL REQUIREMENTS ON XENOTRANSPLANTATION

Xenotransplantation refers to procedure that uses living animal cells or tissues for human therapeutic purposes. Non-viable animal tissue such as porcine heart valves and bone has been used for many years, offsetting limited supply of human equivalents. One example is pancreatic islets intended to treat diabetes.

Xenotransplantation involves the transplantation, implantation, or infusion into a human recipient of either:

a. live cells or tissues from animal source; or
b. human body fluids, cells or tissues that have had *ex vivo* contact with live animal cells or tissues (e.g. extracorporeal perfusion)

[US FDA (2001) definition]

Examples of xenotransplantation products:

a. The use of mouse cells as feeder layer fits part (b) of this definition. Even if the feeder layer cells are irradiated to render them non-proliferative, they are still regarded as living cells and within the definition of xenotransplantation.
b. Xenotransplantation products must be alive, and circulation and return of patients' blood must occur through live non-human cells. For example, human skin cells grown outside the body on a layer of non-human cells and then used in humans for skin reconstruction can also be considered a xenotransplantation product.
c. Xenotransplantation products include those from transgenic or nontransgenic non-human animals and composite products that contain xenotransplantation products in combination with drugs or devices. These include but are not limited to, porcine fetal neuronal cells, encapsulated porcine islet cells, encapsulated bovine adrenal chromaffin cells.

Xenotransplantation products are considered to be biologics, or combination products that contain a biological component. Accordingly, xenotransplantation products are subject to evaluation, regulations governing clinical investigations and product approval as of any CGTP.

The use of animal cells and tissue in the manufacture of cell therapy products requires that the tissue be sourced in a controlled and documented manner from designated-free animals bred and raised in captivity in countries or geographic regions that have appropriate disease prevention and control systems.

The concept of cellular xenotransplantation faces many challenges, including the potential for zoonotic disease transmission to human, and the fact that most animals have shorter lifespan than humans, so their tissues age at a different rate. In addition, a risk of recombination or reassortment of source-animal infectious agents, such as viruses, with non-pathogenic or endogenous human infectious agents to form new pathogenic entities exists.

It is obvious that for the use of xenogeneic cells much more stringent requirements have to be fulfilled according to the increased risk profile. In the EU, the applicable guidelines exclude the use of primary xenogeneic cells; only well-defined and characterised cell lines can be taken into considerations. Hence, a tiered approach to regulation of xenotransplantation products based on degrees of risk and levels of surveillance appropriate to that risk.

The main scientific and technical issues identified so far concern the sourcing and testing of animals, manufacture, quality control, as well as the non-clinical and clinical development of xenogeneic cell-based products. Relevant public health aspects are discussed and measures to ensure a proper surveillance for infections, including zoonosis are required.

Overall, the general principles of CGTPs regulation may apply to products using animal tissues as the starting material, as the key objective is to ensure that the product to be administered is of acceptable quality and standard, and free from contamination.

Table 5: Overview on risks associated with xenotransplantation

Area	**Risk**
Patient	Recipients/ patients immunocompromised
	Direct chronic contact
	Normal first line of defence against infection, such as skin and mucosal surfaces, circumvented.
Infection	Zoonotic infections of humans e.g *Toxoplasma* spp., *Salmonella* spp.
	Experience with human allografts; transmission of HIV,CJD,HBV,HCV
Aggravating factors	Varying incubation periods and possible clinical latency of virus

Area	Risk
	Transmission of organisms pathogenic in humans that may not be pathogenic or even detectable in the source animal
	Recombination of viruses with non-pathogenic human infectious agents to form new pathogens
Public/ community	Infections originating in animals known to infect and be transmitted between humans e.g. HIV
	Transmission of infections from patients to close contact and eventually to general public

HIV = human immunodeficiency virus
CJD = Creutzfeldt-Jakob disease
HBV = hepatitis B virus
HCV = hepatitis C virus

The principal concern is the potential for the transmission of infectious disease from animals to humans. This concern relates not only to the recipient of the xenotransplantation, but also extends to the general public because of the potential for subsequent transmission. Accordingly, during the development and approval of xenotransplantation products much stricter requirements have to be met to safeguard against these increased safety concerns. These specific regulatory requirements apply for xenotransplantation products:

a. Appropriate clinical and scientific expertise of the xenotransplant research team and facility
b. Stringent requirements regarding animal facilities, animal procurement and pre-transplantation animal source screening
c. Risk minimisation precautions during all steps of production
d. Thorough health surveillance program
e. Very comprehensive informed consent and patient education process
f. Long term or even life-long surveillance of xenotransplant recipients regardless of outcome of the clinical trial or the status of the graft or other xenotransplantation products
g. Xenotransplantation recipients to refrain from blood donation
h. Biological specimens archived for public health investigations and for use by sponsor in conduct of surveillance of source animals and xenotransplantation recipients
i. Archiving of health records and biologic specimens to be maintained for 30 years

International efforts to harmonise xenotransplantation should be aimed at the development of reasonable and appropriate methods in recognition of a growing body of evidence and experience regarding the safety of this therapy, and be framed within existing public health monitoring and surveillance systems.

As this guideline is not meant to cover in sufficient details of the requirements for xenotransplantation product, please refer to the following guidelines:

a. US Department of Health and Human Services, Food and Drug administration, Centre of Biologics Evaluation and research. Guidance for Industry : Source Animal, Product, Pre-clinical, and Clinical issues Concerning the Use of Xenotransplantation Products in Humans
b. US Public Health Services Guideline on Infectious Disease Issues in Xenotransplantation
c. EMEA/CHMP/CPWP/83508/2009: Guideline on Xenogeneic Cell-Based Medicinal Products

NOTE:

The focus of the regulation currently is on human cells and tissues. It is acknowledged that more recently, additional efforts and developments have been directed towards xenotransplantation. However, the potential risk for cross-species transmission of infectious agents continues to be debated. We are still cautious of its clinical impact. As such, the relevant party is urged to refer to the specific comprehensive xenotransplantation guidance by US FDA and EMA.

The evaluation requires special disciplines, expertise and skills and as such an application for registration for xenotransplantation products will only be accepted if the product had already been approved by any of our reference regulatory agencies.

ANNEX II. ADDITIONAL REQUIREMENTS ON GENE THERAPY PRODUCTS

Gene therapy involves introducing genetic materials into cells to help prevent or treat a range of diseases such as cancer, degenerative diseases and haemophilia. Cells may be modified *ex vivo* for subsequent administration to humans, or may be altered *in vivo* by gene therapy given directly to the subject. When the genetic manipulation is performed *ex vivo* on cells which are then administered to the patient, this is also a form of somatic cell therapy. The genetic manipulation may be intended to have a therapeutic or prophylactic effect, or may provide a way of marking cells for later identification. Recombinant DNA materials used to transfer genetic material for such therapy are considered components of gene therapy and as such are subject to regulatory oversight.

Gene Therapy Products (GTPs) include recombinant nucleic acid sequence(s) of biological origin, genetically modified virus (es), genetically modified microorganism(s) and cells genetically modified by one or more of these substances.

Gene therapy products can be broadly classified based on the approach to delivery and include the following: (i) viral or non-viral vectors [vectors that harbor the gene(s) of interest but usually without the mechanism to self-replicate *in vivo*]; (ii) nucleic acids in a simple formulation (naked DNA); and (iii) nucleic acids formulated with agents such as liposomes that enhance their ability to penetrate the cell. Where introduction of nucleic acids to cell takes place *ex vivo*, the cell population that is administered becomes the gene therapy product.

The scope of GTPs regulation includes:

a. The addition and expression of a gene for therapeutic purposes
b. The inoculation of nucleic acids for the purpose of developing therapeutic vaccines
c. The transfer of nucleic acids with the aim of modifying the function or the expression of an endogenous gene

As GTPs contain genetic and other material of biological origin, many of the quality guidelines for biotechnological products also apply. Information on all starting materials used for manufacturing of the active substance could be provided. This will include the products necessary for the genetic modification of human or animal cells as well as materials used in culture and preservation of the cells.

As many GTPs consist of, or contain, genetically modified organisms (GMOs), the potential risk of the GMO to the environment also need to be evaluated. An environmental risk assessment (ERA) must be provided. For GTPs consisting of a

GMO, and in particular a viral vector, investigations of sheddings and the risk of transmission to third parties should be provided within the ERA.

A major concern with gene therapy is that it can result in permanent changes that are passed from one generation to the next.

NOTE:

There are still many technical and ethical issues to be addressed and numerous guidelines in development as knowledge and experience evolve in this field.

The general chapter on *Gene Transfer Medicinal Products (GTMPs) For Human Use in European Pharmacopoeia* provide a framework of requirements applicable to the production and control of GTMPs. Guidance specific to manufacturing, processing, purification, characterisation, formulation, and administration of gene therapy products is provided in *Gene Therapy Products, in United States Pharmacopoeias (USP) <1047>.* The European Medicines Agency (EMA) provides multidisciplinary gene therapy guidelines, concept papers and reflection papers on various aspects of gene therapy products including guidelines on follow-up patients, virus and gene therapy vector shedding and transmission, environmental risk assessment, etc.

The evaluation requires special disciplines, expertise and skills and as such Malaysian regulatory authority decided to adopt the guidelines published by the European Medicines Agency (EMA) and United States Food and Drug Administration (US FDA). Subsequently, an application for registration for gene therapy products will only be accepted if the product had already been approved by any of our reference regulatory agencies.

Pre-clinical requirements

As GTPs differ in their complexity and heterogeneity, the extent of non-clinical package varies and will depend on the risk profile of each product. Some requirements are listed below:

a. Pharmacodynamic proof-of-concept (POC) studies should involve appropriate models and relevant animal species, taking target selectivity into account
b. Pharmacokinetics should provide detail analysis of the biodistribution of the GTPs including investigations on its persistence, clearance, mobilisation, shedding and germ line transmission
c. Toxicology should address unintended effects on physiological function, repeated toxicity and immunogenicity

d. Evaluation of safety of the GTPs is required by extensive toxicological testing including analyses on genotoxicity, tumorigenicity, and reproductive and developmental toxicity

Clinical requirements

Human pharmacokinetic studies should include:

a. Shedding studies to address excretion of the GTPs
b. Biodistribution studies
c. Pharmacokinetic studies of the product and the gene expression moieties (e.g. expressed proteins or genomic signatures)

Human pharmacodynamic studies should address the expression and function of the nucleic acid sequence following administration of the product.

Efficacy

The “proof-of-concept” might be desirable and sometimes necessary. Where the mechanism of action is established and the condition to be treated is common, it is sensible to establish efficacy in small studies before undertaking a large confirmatory trial. Dose finding is one of the most important aspects.

Safety studies should address the following aspects:

a. Emergence of replication-competent vector
b. Emergence of new strains
c. Re-assortment of existing genomic sequences
d. Neoplastic proliferation due to insertional mutagenicity

Follow-up of efficacy and safety

As treatment of gene therapy could be curative, maintenance of efficacy is important. Follow-up of safety post-marketing is important. As for efficacy, the duration and nature of the follow-up will depend on the disease and its prognosis.

To help applicants developing gene therapy products, EMA has issued several guidelines as the following:

a. Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products.

b. Non-clinical studies required before first clinical use of gene therapy medicinal products.
c. Non-clinical testing for inadvertent germline transmission of gene transfer vectors.
d. Follow-up of patients administered with gene therapy medicinal products
e. Scientific requirements for the environmental risk assessment of gene-therapy medicinal products

REFERENCES ON CGTPs REGULATION

Malaysia

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2. Private healthcare facilities and services act 1998 (Act 586)
3. Drug Registration Guidance Document (DRGD), National Pharmaceutical Regulatory Agency
4. National guidelines for haematopoietic stem cell therapy
5. National Standards For Stem Cell Transplantation
6. Guidelines for stem cell research and therapy
7. National standards for cord blood banking and transplantation
8. Medical Device Authority. Combination products – List of reference documents. In Medical Device Authority
9. Biosafety Act, 2007
10. Guideline on Good Distribution Practices
11. Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders

PIC/S Guideline

1. PIC/S Guide to Good Manufacturing Practice for Medicinal Products (Part I)
2. PIC/S Guide to Good Manufacturing Practice for Medicinal Products (Part II)
3. PIC/S Guide to Good Manufacturing Practice for Medicinal Products Annexes

WHO (Quality, Clinical & Combined Guidelines)

1. WHO guidelines on tissue infectivity distribution in transmissible spongiform encephalopathies
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4. Statement from the xenotransplantation advisory consultation, Geneva 18-20 April 2005
5. WHO guiding principles on human cell, tissue and organ transplantation
6. WHO Expert Committee on Biological Standardization: Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterisation of cell banks, WHO TRS No. 978 (61st Report)

ICH (Quality, Nonclinical & Clinical)

1. Q2 Validation of analytical procedures
2. Q5A: Guideline on quality of biotechnological products: viral safety evaluation of biotechnology product derived from cell lines in of human or animal origin
3. Q5B: Analysis of the expression construct in cells used for production of r-DNA derived protein products
4. Q5C: Stability testing of biotechnological/biological products
5. Q5D: Derivation and characterisation of cell substrates used for production of biotechnological/ biological products
6. Q5E: Comparability of biotechnological/biological products subject to changes in their manufacturing process
7. Q6B: Specifications: test procedures and acceptance criteria for
8. biotechnological/biological products
9. Q9: Quality risk management
10. M6: Virus and gene therapy vector shedding and transmission
11. S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals
12. S9: Nonclinical evaluation for anticancer pharmaceuticals
13. E2C: Periodic benefit-risk evaluation report
14. E2E: Pharmacovigilance planning
15. E2F: Development Safety Update Report
16. E6: Good Clinical Practice
17. E8: General Considerations for Clinical Trials
18. E9: Statistical Principles for Clinical Trials
19. E10: Choice of control group and related issues in clinical trials
20. E11: Clinical investigation of medicinal products in the pediatric population

U.S. FDA (Quality, Nonclinical, Clinical & Combined)

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2. Guidance for industry: Human Gene Therapy for Neurodegenerative Diseases
3. Guidance for Industry: Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products
4. Guidance for Industry: Human Gene Therapy Products Incorporating Human Genome Editing
5. Guidance for Industry: Manufacturing Considerations for Licensed and Investigational Cellular and Gene Therapy Products During COVID-19 Public Health Emergency
6. Guidance for industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

7. Guidance for industry: Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up
8. Guidance for industry: Human Gene Therapy for Hemophilia
9. Guidance for industry: Human Gene Therapy for Rare Diseases
10. Guidance for industry: Human Gene Therapy for Retinal Disorders
11. Guidance for industry: Evaluation of Devices Used with Regenerative Medicine Advanced Therapies
12. Guidance for industry: Expedited Programs for Regenerative Medicine Therapies for Serious Conditions
13. Guidance for Industry and Food and Drug Administration Staff: Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use
14. Guidance for industry: Recommendations for Microbial Vectors Used for Gene Therapy
15. Guidance for industry: Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products
16. Guidance for industry: Considerations for the design of early-phase clinical trials of cellular and gene therapy products
17. Guidance for Industry: Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products
18. Guidance for industry: Use of donor screening tests to test donors of human cells, tissues and cellular and tissue-based products (HCT/Ps) for Infection with *Treponema pallidum* (Syphilis)
19. Guidance for industry: Use of nucleic acid tests to reduce the risk of transmission of West Nile Virus from donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps)
20. Guidance for industry: Current good tissue practice (cGTP) and additional requirements for manufacturers of human cells, tissues, and cellular and tissue based products (HCT/Ps)
21. Guidance for industry: Class II special controls guidance document: cord blood processing system and storage container
22. Guidance for industry: Potency tests for cellular and gene therapy products (
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30. Guidance for industry: Screening and testing of donors of human tissue intended for transplantation
31. Guidance for the submission of chemistry, manufacturing, and controls information and establishment description for autologous somatic cell therapy products
32. Points to consider in the characterisation of cell lines used to produce biologicals
33. Guidance of industry: Preclinical assessment of investigational cellular and gene therapy products
34. Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection
35. Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products
36. Guidance for industry: Clinical considerations for therapeutic cancer vaccines
37. Guidance for industry: Non-Inferiority Clinical Trials to Establish Effectiveness
38. Guidance for industry: Adaptive design clinical trials for drugs and biologics
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40. Guidance for industry: cGMP for phase 1 investigational drugs
41. Guidance for industry: Clinical trial endpoints for the approval of cancer drugs and biologics
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46. CFR – 21 – Part 1271: Human cells, tissues, and cellular and tissue-based products

47. Guidance for industry: Preparation of IDEs (Investigational Devices Exemption) and INDs for products intended to repair or replace knee cartilage
48. Guidance for industry: Cellular therapy for cardiac disease
49. Guidance for industry: Considerations for allogeneic pancreatic islet cell products
50. Guidance for industry and FDA staff: Early development considerations for innovative combination products
51. NIH Guidelines for Research Involving Recombinant DNA Molecules
52. Guidance for industry: Guidance for human somatic cell therapy and gene therapy
53. A proposed approach to the regulation of cellular and tissue-based products (62 FR 9721)
54. Guidance on applications for products comprised of living autologous cells manipulated *ex vivo* and intended for structural repair or reconstruction (61 FR 26523)
55. FDA guidance concerning demonstration of comparability of human biological product, including therapeutic biotechnology-derived products
56. Public Health Service (PHS) guideline on infectious disease issues in xenotransplantation
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