



**NATIONAL PHARMACEUTICAL CONTROL BUREAU  
MINISTRY OF HEALTH MALAYSIA**

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

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

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## **FOREWORD BY SENIOR DIRECTOR OF PHARMACEUTICAL SERVICES DIVISION, MINISTRY OF HEALTH, MALAYSIA**

Development of biological medicines has been extremely rapid and the potential of such products for improving health care on a global scale is immense. Cell and gene therapies have been at the forefront of biotechnology research during the past decade, providing for a cornucopia of new strategies for the treatment of diseases such as immune-mediated chronic disease, some forms of cancer as well as for repair and regeneration, and to this effect, many lives have been transformed.

The “Age of Cell Therapy” has arrived. With a robust pipeline of products in late stages of clinical development and moving towards licensure whilst some products already achieving regulatory approval, strongly indicates that the cell therapy industry is poised to merge as a distinct healthcare sector. Cell therapy has the potential to be the fourth pillar in health care, together with small molecules, biologicals, and devices. Cell therapy fits within the large and even more diverse regenerative medicines industry.

Regenerative medicines and cell-based therapies continue to engender bold prognostications about how they could revolutionise healthcare. Living, delicate and diverse cells are being incorporated as active agents and delivery for a broad range of emerging therapeutic strategies. Stem cells represent seemingly limitless clinical applications. Yet, along with this great promise come numerous challenges and ground-breaking therapies cannot reach those who need them without successful commercialisation. Their extreme intrinsic complexity in terms of substance, characterization, manufacture, their dynamic mode of action, potential risks and the “idiosyncrasies”, require us to perhaps think and act in new ways *vis-a-vis* a new regulatory paradigm to ensure consistency, quality, safety and efficacy.

Gene therapies have travelled a difficult road so far, with a mixture of promise and disappointment. But their story is far from over. Increasing evidence suggests that gene therapy can provide long-term therapeutic effects for patients suffering from genetic and complex disorders. Consequently, momentum in the field is building up, resulting in the first gene therapy product licensure in the European Union in 2012.

The history of biopharmaceutical sector is one of continual invention and reinvention, of regulation / business models that have adapted to weather uncertain product features and shifting economic fortunes. Taking full advantage of the unique properties of these cells and genes will require advances in or knowledge and expertise of their inner workings as well as development of new approaches to their large scale production and associated regulatory scrutiny and oversight. We must also take time to orchestrate our efforts towards producing high quality talent,

regulation, deep expertise and up-skilling of evaluators / regulators to meet our capacity building initiatives.

The regulatory framework for cell and gene therapy products (CGTPs) attempts to address the unique characteristics of these products through a suitably adjusted set of principles. CGTPs are subject to the same Investigational New Drug (IND) and product registration / approval process as any other biologics. It is hoped that a productive balance between the need to protect public health while enhancing access can be attained.

The development of CGTPs guidance document and guidelines for registration in Malaysia had engaged relevant stakeholders from various government agencies, research/academic and treatment institutions, pharmaceutical industries, manufacturers / importers via the formation of the Technical Working Group (TWG-CGTPs), chaired by National Pharmaceutical Control Bureau (NPCB), Ministry of Health Malaysia. The challenging task has been culminated in the publication of this guidance document. The regulation fundamentally support good clinical care by increasing safety and control, and enable good science by improving the quality and reliability of data in addition to intensive monitoring for safety and efficacy and most importantly is pragmatic. These outcomes are in everyone's interest.

To complement Malaysia's aim to achieve scientific excellence, innovations and to fully exploit the potential of biotechnology, new research endeavours in personalized medicines and stem cell therapy to promote new sources of growth and decrease dependence on outside sources. Hence, under the Bioeconomy Transformation Programme (BTP), Stem Cells and Regenerative Medicines has been identified as one of the 10 Entry Point Projects (EPPs). I am convinced that we must strengthen and enhance our efforts and partnerships at an international level - constantly review our capacity building initiatives to meet targets and consistently build on niche areas of specialties.

Biotechnology has opened up a new and exciting vista to regulators alike, towards paradigm-shifting to healthcare field looking at areas of unmet need. This calls for a plausible match of the regulatory oversight with biotechnological advancements and innovations to ensure adequate quality, efficacy and safety of novel products. Thus, I believe that regulatory science and regulation that is transparent, science based and forward-looking is key. Science, even with broad-band, takes time and due diligence, indeed, the regulation of CGTPs is still evolving, as befits a relatively young developing field.

As reforms move forward, worldwide regulatory convergence and sharing of knowledge and experience will be vital to effective regulation, since safety issues have no borders. The success of CGTPs depends on putting our patient's needs and safety first as our primary objective of public health protection, together with committed stakeholder and the government's keen interest/support - a win-win outcome is envisaged. In corollary, this will further enhance and promote a dynamic and competitive knowledge-based economy for healthcare biotechnology in Malaysia.

**DATO' EISAH A. RAHMAN**

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**January 2015**

## **FOREWORD BY CHAIRMAN OF TECHNICAL WORKING GROUP ON CELL AND GENE THERAPY PRODUCT**

It has been proclaimed that regenerative medicine would serve as the fourth pillar to support healthcare needs, following the establishment of pharmaceutical, biological and medical device products. The advent of cell and gene therapies as products of translational science in regenerative medicine presents challenges to regulators worldwide. Several cell therapy products have been approved for marketing, namely ChondroCelect® in the European Union and Carticel® in the United States. The European Medicines Agency (EMA) has granted a marketing authorisation for a gene therapy product, Glybera®.

Talks on regulation on cell and gene therapy products (CGTPs) in Malaysia have been gathering steam since 2009. A series of internal discussions within the National Pharmaceutical Control Bureau (NPCB) led to the formation of a Technical Working Group (TWG) in 2012, tasked to formulate strategies on regulation of CGTPs in Malaysia. The TWG is represented by all stakeholders from government agencies, research and treatment institutions, pharmaceutical product manufacturers/importers, including those from the local cell based industry. The discussions mainly addressed the Ministry of Health's concern on unregulated use of CGTPs leading to adverse health implications.

Although the regulation of CGTPs requires an inter-agency approach even within the Ministry of Health and calls for arduous coordination among relevant agencies such as NPCB and the Medical Practice and Development Divisions, I am immensely proud that the challenging journey has now culminated in the publication of this guidance document. As such, I hope the recommendations contained within this document serve well as a future direction to regulators, product developers and medical practitioners alike in facing the new era of regenerative medicine.

I wish to convey my deepest gratitude to the NPCB team led by the Section for Biologic Product Registration for their laborious effort in formulating this document. Many thanks to all stakeholders for their critical opinions throughout the drafting process. Congratulations to all on a job well done!

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**IN APPRECIATION:  
FOREWORD BY PRIMARY AUTHOR OF GUIDANCE DOCUMENT**

Guidance document is meant to provide assistance to applicants/marketing authorization holders (MAH) on how to comply with the governing acts and regulations. It also clearly outlines the regulatory framework and registration requirements and/or process with the necessary guidelines to applicants/marketing authorization holders

Guidance document also provides assistance to stakeholders on how National Pharmaceutical Control Bureau's (NPCB) mandates and objectives should be implemented in a manner that is fair, consistent and effective. It is important to note that NPCB reserves the right to request information or material, or define conditions not specifically described in this document, in order to ensure the safety, efficacy or quality of a therapeutic biologic product including Cell and Gene Therapy Products (CGTPs). NPCB is committed to ensure that such requests are justifiable and that decisions are clearly documented.

For the purpose of this document, the term Cell and Gene Therapy Products (CGTPs) will be used. These include somatic cell therapy products, tissue engineered products and gene therapy products as well as combined products.

It is universally agreed that CGTPs have an enormous potential of revolutionizing therapy. CGTPs show great promise and offer ground-breaking new treatment opportunities for diseases, for regenerative and replacement medicines, thereby targeting many unmet medical needs.

The key benefits of regulating CGTPs separately under this framework will:

- safeguard public health and patient protection
- ensure the level of regulation applied matches the level of risk posed by specific products (tiered risk-based approach)
- provide a more flexible framework to respond to changes in technology
- provide regulatory requirements that are unique to CGTPs which is cross-boundary in nature. Hence, call for integrated regulatory oversight for quality, efficacy and safety of the product
- reduce the ambiguity about what should be included or excluded from the regulation.

The purpose of this guidance document is:

- to outline the concept and basic principles of CGTPs;
- to introduce the registration framework and guidelines to be applied;
- to provide applicants with a "user guide" for the relevant scientific data and information, in order to substantiate the claim quality, safety and efficacy of the product.

Due to the unique and diverse nature of cell and gene therapy products therefore – they do not lend themselves to a "one size fits all" concept of product development and regulation. Each product is unique and merits attention.

It is important to work together with regulatory authority in the course of product development, but in the case of CGTPs it is imperative. In cognizance, that stakeholders may have limited capacity to navigate the required regulatory procedures, approach, compliance and expectations. Our experience demonstrates that transparent and open dialogue with all relevant stakeholders is key to put in place a robust and pragmatic regulatory framework in this emerging field whilst creating and promoting a patient-centred approach.

As such, I hope the information and guidance contained within this document serve well to assist and harness the complexity as well as future direction to regulators, product developers and medical practitioners alike in facing the new era of regenerative medicine.

**ARPAH BT. ABAS**

**Head of Biologics Section, NPCB (until May 2015)**

**January 2015**

**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, March 1998)
2. Guideline on human cell-based medicinal products (EMEA/CHMP/410869/06) (EMA, January 2007)
3. Reflection paper on classification of ATMPs (EMA, April 2012)
4. Draft Guidance for Industry and FDA Staff: Minimal manipulation of human cells, tissues, and cellular and tissue-based products (U S FDA, December 2014)
5. Annex 2 Manufacture of biological medicinal substances and products for human use, PE 009-11 (Annexes) (PIC/S, March 2014)
6. Guidelines for the clinical translation of stem cells (ISSCR, December 2008)
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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](https://mact.org.my/reg_about_mctpr.html) . Accessed on 17 October 2014

## 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 Cosmetic Regulations
CGTP	Cell and Gene Therapy Product
CT	Cellular Therapies
CTP	Cell Therapy Product
DCA	Drug Control Authority
DNA	Deoxyribonucleic Acid
ERA	Environmental Risk Assessment
ESC	Embryonic Stem Cell
EU	European Union
EMA	European Medicines Agency
GMO	Genetically Modified Organism
cGMP	current Good Manufacturing Practice
cGTP	current Good Tissue Practice
GMTP	Gene Modified Therapy Product
GTP	Gene Therapy Product
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
MOH	Ministry Of Health
MSCs	Mesenchymal Stromal/Stem Cells
NCE	New Chemical Entity
NRA	National Control Authority
NPCB	National Pharmaceutical Control Bureau
PK/PD	Pharmacokinetic/Pharmacodynamic
Ph. Eur.	European Pharmacopeia
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
PSUR	Periodic Safety Update Reports
QC	Quality Control
QWP	Quality Working Party
RM	Regenerative Medicines
SC	Stem cells
US FDA	United States Food and Drug Administration
RMP	Risk Management Plan
WCB	Working Cell Bank
WHO	World Health Organisation

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## 1.0 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 posts some difficult-to-appraise risks, such as tumourigenicity, immunogenicity, *in vivo* migration of transfused cells and reversibility of administration in the event of an intolerable reaction
- In addition to the requirements of current Good Manufacturing Practice (cGMP), the principles of current Good Tissue Practice (cGTP) need to be applied in the quality assurance of a CGTP.

In consideration of the unique challenges of CGTP regulation mentioned above, the Malaysian CGTP 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.

This guidance document should be read together with its accompanying ***Good Tissue Practice Guideline published by the Centre for Compliance & Licensing, 2<sup>nd</sup> Edition, December 2015.***

In summary, the 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 CGTP registration will allow NPCB 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.

## **2.0 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 medicinal products. CGTPs fit within the meaning of medicinal products under the Sale of Drugs Act 1952: Control of Drugs And Cosmetic Regulations 1984 [P.U.(A) 223/84]. And in accordance to the statutory provisions CGTPs 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 sections of the **Control of Drugs and Cosmetic Regulations 1984 (CDCR 1984)** and the relevant sections of other applicable NPCB guidance documents and guidelines, as listed below (available at <http://www.bpfk.gov.my>):

- a. Drug Registration Guidance Document (DRGD), First Edition – January 2013, including Guidelines on registration of biologics, DRGD (Appendix 3)
- b. Guideline for Submission of Analytical Method Validation Documents (NPCB)
- c. Malaysian Guidelines for the Conduct of Bioavailability and Bioequivalence Studies (NPCB, September 2000)
- d. Malaysian Guidelines for Good Clinical Practice, 3rd Edition (MOH, October

2010)

- e. Malaysian Variation Guideline for Pharmaceutical Products (NPCB, 2013)
- f. Guidance Document on Foreign GMP Inspection (NPCB, August 2014)
- g. Guidance Note for Biological Products Manufacturing Facility Establishment in Malaysia (NPCB, May 2015)
- h. Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption, Sixth Edition (NPCB, October 2014)
- i. Annex 1, Part 11 – A Guide Manual for Adverse Event Reporting (NPCB)
- j. The ASEAN Common Technical Dossier (ACTD) for the Registration of Pharmaceuticals for Human Use (ASEAN, September 2002)

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 CGTP regulatory framework:

- a. Private Healthcare Facilities and Services Act 1998 (Act 586)
- b. Guidelines For Stem Cell Research And Therapy 2009 MOH/P/PAK/177.08(GU)
- c. National Standards For Stem Transplantation 2009 MOH/P/PAK/188.09(BP)
- d. National Guidelines For Haemopoietic Stem Cell Therapy 2009 MOH/P/PAK/179.09(GU)
- e. National standards For Cord Blood Banking And Transplantation 2008 MOH/P/PAK/131.07(BP)
- f. Checklist For Research On Stem Cells and cell-based Therapies (NSCERT 2009)
- g. Guidelines On Importation And Exportation Of Human Tissue And/Or Body parts (CDC 2006)
- h. Medical Device Act (2012) (Act 737)

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 **14. ANNEX** 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), etc.

## 2.2 ABOUT THIS FRAMEWORK

The regulatory framework aims to provide a clear and predictable pathway for CGTPs based on internationally benchmarked regulations. NPCB 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. Included are some regulatory procedures and guidelines in new areas such as current Good Tissue Practice (cGTP).

The cross-boundary nature 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:

- The clinical use/medical procedure of the product will be under the ambit of Medical Development Division and Medical Practice Division of the Ministry of Health, Malaysia
- 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
- NPCB will ensure the medicinal product’s quality, efficacy and safety.

Only one agency (NPCB/MDA) will take charge of a product registration at any one time. There will be no joint evaluation involving both agencies unless due to extraordinary circumstances. An application for product classification shall be submitted to NPCB and assignment will depend on the primary mode of action / principle mechanism of action as claimed. For products not clearly defined as a drug/cosmetic or a medical device, assignment will be referred to the Medical Device – Drug-Cosmetic Interface (MDDCI) Product Classification Committee, jointly held by NPCB and MDA. Please refer to the ***Guideline for Registration of Drug-Medical Device and Medical Device-Drug Combination Products, First Edition, November 2015*** and ***Section 1.4 Drug Registration Guidance***

**Document (DRGD), First Edition – January 2013** for more information.

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 CGTP 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.

## **3.0 SCOPE**

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

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

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

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 CGTP involves their use.

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

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

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

- Fresh viable human organs, or parts of human organs, for direct donor-to-host transplantation.
- Fresh viable human haematopoietic stem/progenitor cells for direct donor-to-host transplantation for the purpose of haematopoietic reconstitution.
- Labile (fresh) blood and blood components (e.g. fresh frozen plasma)
- Unprocessed reproductive tissues (e.g. sperm, eggs, embryos for *in vitro* fertilization (IVF) and other assisted reproductive technology procedures)
- Secreted or extracted human products (e.g. milk, collagen)
- Samples of human cells or tissues that are solely for diagnostic purposes in the same individual
- *In vitro* diagnostic devices

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

For other types of stem cell product/therapy **not within the scope** of this framework, please refer to:

- a. National Standards For Cord Blood Banking And Transplantation *January 2008 MOH/P/PAK/131.07(BP)*
- b. National Guidelines For Haemopoietic Stem Cell Therapy *July 2009 MOH/P/PAK/179.09 (GU)*
- c. National Standards For Stem Cell Transplantation: Collection, Processing,

## Storage And Infusion Of Haemopoietic Stem Cells And Therapeutic Stem Cells, July 2009 [MOH/P/188.09(BP)]

The regulatory framework on CGTPs is broadly divided into three parts: cell therapy, xenotransplantation, and gene therapy. Cellular therapeutics that incorporate gene repair or genetic modification must adhere to regulatory guidelines set forth for both cell therapy and gene therapy products.

In Malaysia, an application to administer an unregistered product may be obtained from the Director-General of Health / Senior Director of Pharmaceutical Services. This pathway can apply to CGTPs for compassionate use. For application procedures, please refer to the website of Pharmaceutical Services Division at <http://www.pharmacy.gov.my/v2/ms/entri/permohonan-memperolehi-menggunakan-ubat-memerlukan-kelulusan-khas-ketua-pengarah-kesihatan-malaysia.html> .

For CGTPs indicated in rare diseases, an application for Orphan Product status may be submitted to NPCB. As the establishment of an Orphan Product registration pathway is underway, NPCB will publish more information on Orphan Product registration on its website (<http://www.bpfk.gov.my>) in the near future. At present, some information is available in Section 5.1.4 **Drug Registration Guidance Document (DRGD), First Edition – January 2013**.

### 4.0 DEFINITIONS

#### 4.1 CELL THERAPY PRODUCTS

**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.

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.

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. However, *in vitro* differentiation often generates 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 re-acquire 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.

**NOTE:**

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.

## **4.2 GENE THERAPY PRODUCTS**

A gene therapy medicinal product means a biological medicinal 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**:

- vaccines against infectious diseases
- \*chemically synthesised nucleic acids (e.g. RNA, DNA, oligonucleotides)

The final medicinal product may contain as an integral part 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 COMBINED PRODUCTS**

A combined 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, First Edition, November 2015*** and ***Section 1.4 Drug Registration Guidance Document (DRGD), First Edition – January 2013*** 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 medicinal product is to be considered as a gene therapy medicinal product, further guidance can be found in the ***Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products (CPMP/BWP/3088/99, EMA, April 2001)***.

#### 5.0 ORGANISATION OF DATA/DOSSIER

As the majority of cell therapy products are unique, the manufacturer must understand both the science behind the specific cell product and the regulations in order to successfully communicate with the authorities. Though the regulations are written in general terms to be applied to all cell therapy products, they can be tailored to an individual product with good communication and sound, data-driven scientific justification.

As regards to the amount/kind of data requirements for a CGTPs 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.

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 NPCB. An approval for a Clinical Trial Import Licence (CTIL) or a Clinical Trial Exemption (CTX) is mandatory before an unregistered CGTP is administered to human trial subjects in Malaysia.

To register a CGTP, an application for product registration must be filed at NPCB. Such approvals require sufficient data that the investigational product is of acceptable quality, and is safe and effective to humans.

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. Exceptions to this rule may include lower risk haematological products that qualify as being minimally manipulated, perform the same basic function in the donor as the recipient (homologous use), not to be combined with other agents and not have a systemic effect. Such products will be regulated clinically under the Medical Practice/Development Divisions, Ministry Of Health Malaysia. They do not require pre-market approval and are regulated by site registration including establishment of cGTP.

## **6.0 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 offsprings)”.

“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* vs. *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 nonstructural 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 (commonly defined as cells maintained in culture under non-proliferating conditions for short periods of time, normally less than 48 hours) 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 nonstructural tissues, and examples of minimal/ more than minimal manipulations for each tissue type, refer ***Draft Guidance for Industry and FDA Staff: Minimal manipulation of human cells, tissues, and cellular and tissue-based products (December 2014)***.

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).

## **7.0 RISK CLASSIFICATION OF CELL THERAPY PRODUCTS**

The risk-based approach to CTPs 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:

### **7.1 CLASS I: LOWER RISK CELL THERAPY PRODUCTS**

For lower risk products, the regulatory framework focuses on minimising the risk of transmission of infectious diseases. A product eligible for regulation as Class I is not subjected to premarket review requirements or approval. However, the product must be listed at the practitioner's premises. The product is further regulated by: (i) site/facility licensure and listing by the Medical Practice Division under the purview of the Private Healthcare Facilities and Services Act 1998 (Act 586) (ii) donor screening and testing (iii) Good Tissue Practices (please refer to ***National Pharmaceutical Control Bureau, Ministry of Health: Good Tissue Practice Guideline, 2<sup>nd</sup> Ed., December 2015***) (iv) labelling (v) adverse event reporting and; (vi) inspection and enforcement.

To be a Class I CTP, the product must 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:

- 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
- 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.

Some e.g. of homologous use:

- A heart valve is transplanted to replace a dysfunctional heart valve. This is homologous because the donor heart valve performs the same basic function in the donor as in the recipient of ensuring unidirectional blood flow within the heart.
- Pericardium is intended to be used as a wound covering for dura mater defects. This is homologous use because the pericardium is intended to repair or reconstruct the dura mater and serve as a covering in the recipient, which is one of the basic functions it performs in the donor.

Some e.g. of non-homologous use:

- using CD34+ HSCs in repairing heart function
- using adipose or bone marrow MSCs to treat neurological conditions

- using an adipose-derived MSC product as a bone graft substitute for the repair, replacement, or reconstruction of musculoskeletal defects
- using a human amniotic membrane product for bone tissue replacement to support bone regeneration following surgery to repair or replace bone defects or other orthopaedic indications.

The document entitled ***Draft Guidance for Industry and FDA Staff: Homologous use of human cells, tissues, and cellular and tissue-based products (October 2015)*** may be referred.

## **7.2 CLASS II: HIGHER RISK CELL THERAPY PRODUCTS**

If a cell therapy product does not meet all the four criteria in Class I, then the product will fall under Class II. A Class II product 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. Both cGTP and cGMP are required. The product dossier should follow the ACTD format. Please refer to ***NPCB’s Drug Registration Guidance Document – Appendix 3: Guidelines on Registration of Biologics, First Edition, January 2013*** for general information and requirements for registration of biologic products in Malaysia. For CTIL/CTX requirements, please refer to Malaysian Guideline for Application of CTIL/CTX, 6<sup>th</sup> Edition (NPCB, 2015).

In the clinical development of a Class II product, 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 on 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 medicinal product and would be subject to this framework.

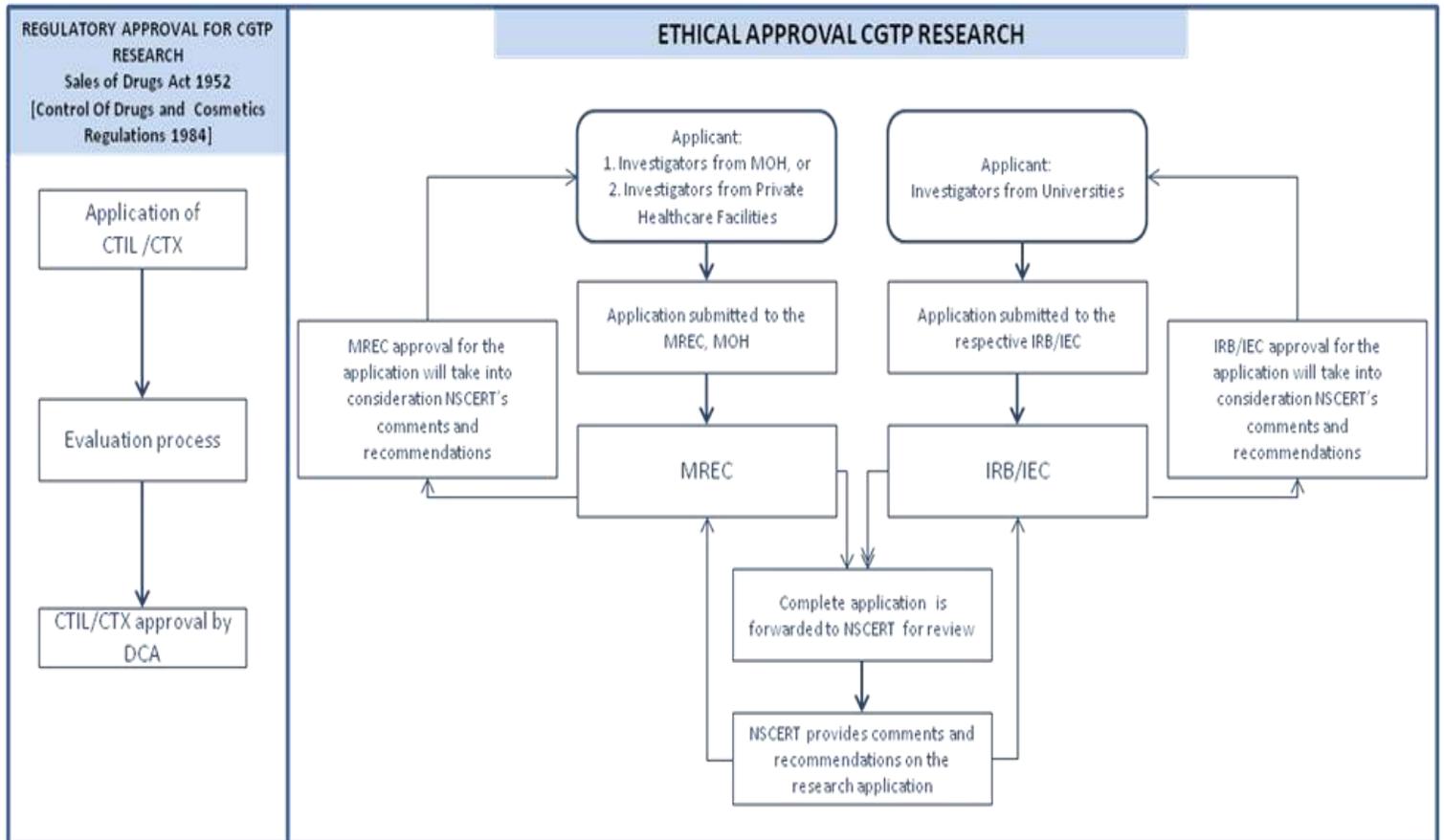
### **Note:**

NPCB reserves its full jurisdiction on assignment of product classes – this means that all classification activities must be conducted with the agreement of NPCB. In addition, a risk-based classification approach should be adopted, i.e. product presumed to present the highest level of risk until demonstrated otherwise.

### 7.3 MATRIX ON REGULATORY FRAMEWORK OF CELL THERAPY PRODUCTS

The following figures summarise the regulatory framework of CGTPs, and include information on relevant local authorities other than NPCB and their processing timelines.

**Figure 1: Clinical trial approval pathway for CGTPs**



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

CTIL = Clinical Trial Import Licence

CTX = Clinical trial Exemption

MOH = Ministry of Health

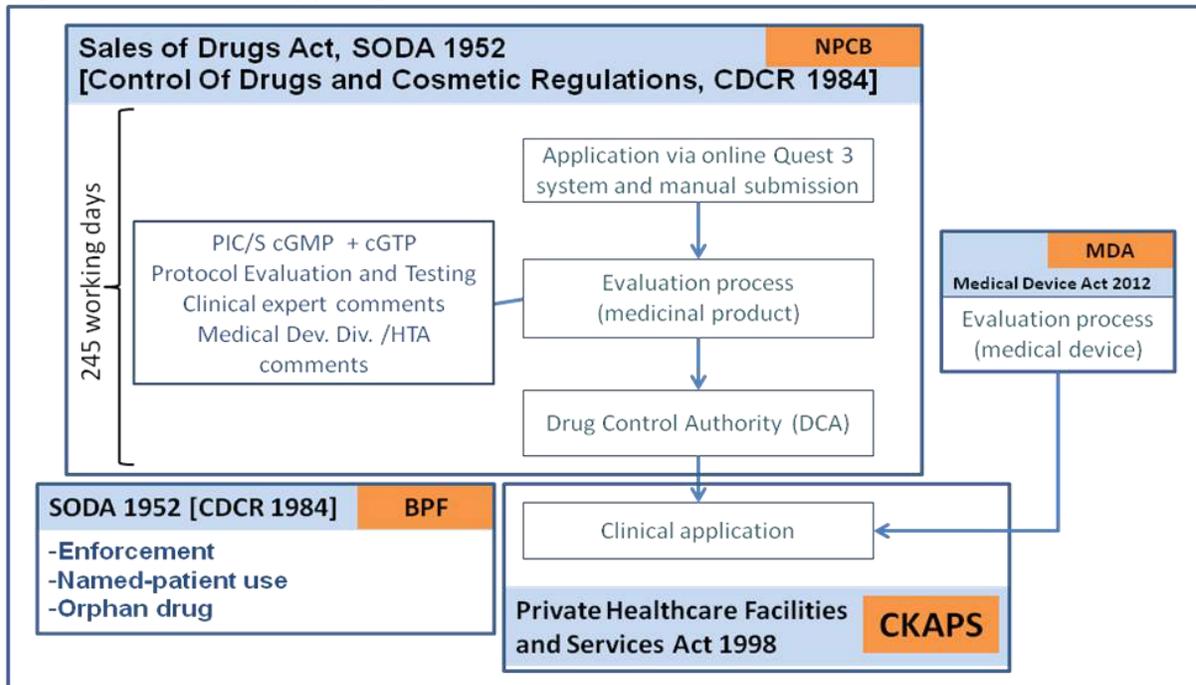
MREC = Medical Research and Ethics Committee

IRB = Institutional Review Board

IEC = Institutional Ethics Committee

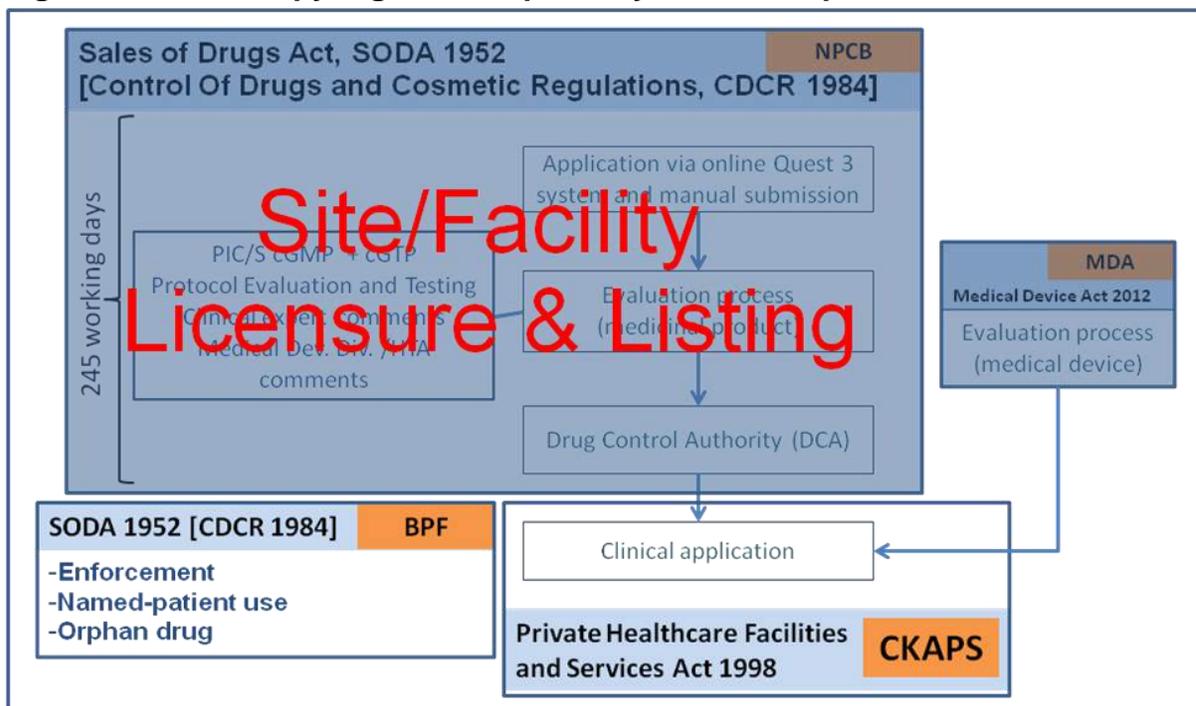
NSCERT = National Stem Cell Research and Ethics Subcommittee

**Figure 2: Cell therapy registration pathway for Class II products**



PIC/S cGMP = Pharmaceutical Inspection Co-operation Scheme  
 HTA = Health Technology Assessment  
 BPF = Bahagian Perkhidmatan Farmasi  
 CKAPS = Cawangan Kawalan Amalan Perubatan Swasta  
 MDA = Medical Device Authority

**Figure 3: Cell therapy registration pathway for Class I products**



## 8.0 QUALITY ASSURANCE FOR CGTPs

Cell based therapies are inherently challenging to current Good Manufacturing Practice (cGMP) 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 cellular therapy products should be in compliance with the principles of current Good Manufacturing Practices (cGMP). The Pharmaceutical Inspection Convention/Scheme (PIC/S) cGMP regulations comprise basic requirements applying to all products as well as annexes with detailed requirements for special types of products. Of particular relevance to CGTPs are:

- Annex 1: Manufacture of Sterile Medicinal Products
- Annex 2: Manufacture of Biological Medicinal Products for Human Use
- Annex 11: Computerised System
- Annex 13: Manufacture of Investigational Medicinal Products
- Annex 14: Human Blood and Plasma Products
- Annex 15: Qualification and Validation

In addition to the requirements of current Good Manufacturing Practices (cGMP), the principles of current Good Tissue Practices (cGTP) need to be applied in the quality assurance of a CGTP. For cGTP requirements, refer to ***Good Tissue Practice Guideline published by the Centre for Compliance & Licensing, 2<sup>nd</sup> Edition, December 2015.***

## PART I. GENERAL REQUIREMENTS

A risk-based approach will be taken in determining the extent of the quality, non-clinical 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: CGTP registration requirements**

General	Requirements of cGTP, cGMP, GCP	
Class	I	II
		Novel Cell and Gene Therapies
<b>Pre-Market Review/Approval</b>	Cell Products Exempted from Marketing Authorisation	Complete CMC, Pre-Clinical & Clinical Data
<b>Compliance with GMP for human and blood tissue standards</b>	Statement on compliance/ GTP (listing of manufacturer)	Only products with current manufacturing licence will be accepted





CMC & Pre-Clinical evaluation



**Investigational Product**



GCP Clinical Trials



<b>Marketing Authorisation</b>	<b>Monograph/product profiling</b>	<b>New Biologic Product</b>
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<b>Post Marketing</b>	Routine Pharmacovigilance	Active surveillance (Patient Registry)
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## 9.0 CHEMISTRY, MANUFACTURING AND CONTROL (CMC)

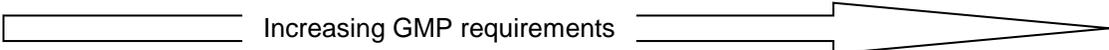
It is imperative to develop appropriate quality management systems for the entire “needle-to-needle” process from collection to transplant, including donation, procurement testing, coding, processing, preservation, storage and distribution of the cells.

All manufacturing steps need to be conducted in a controlled aseptic environment, in accordance with the requirements of ***Annex 2 Manufacture of biological medicinal substances and products for human use, PIC/S March 2014***. 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 cGMP requirements for CGTPs are illustrated in the following table.

**Table 2: Illustrative guide to manufacturing activities for CGTPs**

Type and source of material	Example product	Application of cGMP to manufacturing steps shown in grey			
Human and/or animal sources	Gene therapy: genetically modified cells	Donation, procurement and testing of starting tissue / cells	Manufacture vector and cell purification and processing	<i>Ex vivo</i> genetic modification of cells, Establish MCB, WCB or primary cell lot	Formulation, filling
	Somatic cell therapy		Establish MCB, WCB or primary cell lot	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
	Tissue engineered products		Initial processing, isolation and purification Establish MCB, WCB or primary cell lot	Cell isolation, culture purification, combination with non-cellular components	Formulation, combination, fill
Animal source: non-transgenic	CGTPs immunosera	Collection of plant, organ, tissue or fluid	Cutting, mixing, and /or initial processing	Isolation and purification	Formulation, filling
Virus or bacteria/ fermentation/ cell culture	Viral or bacterial vaccines	Establishment and maintenance of MCB, WCB, MVS, WVS	Cell culture and/or fermentation	Inactivation when applicable, isolation and purification	Formulation, filling
Biotechnology fermentation/ cell culture	Gene therapy vaccines (viral and non-viral vectors, plasmids)	Establishment and maintenance of MCB, WCB, MSL, WSL	Cell culture and/or fermentation	Isolation, purification, modification	Formulation, filling
					

MCB = Master Cell Bank  
WCB = Working Cell Bank  
MVS = Master Virus Seed  
WVS = Working Virus Seed

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 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 CGTP. 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 must 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.**

## **9.1 STARTING AND RAW MATERIALS**

As CGTPs are complex products, the source, origin and suitability of biological starting and raw materials (e.g. cryoprotectants, feeder cells, reagents, culture media, buffers, serum, enzymes, cytokines, growth factors) 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:

- All raw materials of human and animal origin must be stringently sourced and qualified based on product and process-related requirements and acceptance criteria
- 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
- The authenticity, provenance and genotypic/phenotypic characteristics of the source cells must be demonstrated
- The stability and functional integrity of the cells in extended *in vitro* passage must be monitored
- 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

- Any culture reagents prepared in the laboratory should be documented, controlled for quality and released against an established specification
- 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:

- The initial procurement of cell should always be conducted using sterile techniques and universal precautions to minimise the risks of contamination, infection and pathogen transmission
- 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
- 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
- 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 3: Drug Registration Guidance Document, First Edition, January 2013** for relevant checklists to be filled*

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

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

- Medical history and health status of the donor should be investigated for potential further risks to the recipient
- 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
- 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.

### **Organ/tissue dissociation**

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.

### **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 combined 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.  $\beta$ -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 3: Drug Registration Guidance Document, First Edition, January 2013.***

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: Guideline on quality of biotechnological products: Viral safety evaluation of biotechnology product derived from cell lines in of human or animal origin (September 1999):***

- Selection of source of materials and testing for viral contaminants
- Testing the capacity of the production process to remove and/inactivate viruses
- 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.

## **9.2 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:

- 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
- 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 cGMP. 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.
- 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.
- 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).
- 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:

- ICH Q5A: Guideline on quality of biotechnological products: Viral safety evaluation of biotechnological product derived from cell lines on of human or animal origin (September 1999)***

- b. ICH Q5D: Derivation and characterisation of cell substrates used for production of biotechnological/biological products (July 1997)**
- 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, 61<sup>st</sup> Report (2010)**

### **9.3 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 ***Guideline on human cell-based medicinal products (EMA/CHMP/410869/06) (EMA, January 2007)***.

### **9.4 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 validated 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 combined medicinal 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 and 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.

## **9.5 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 combined 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.

## 9.6 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 (March 1999)***. All release testing should be performed using methods validated at the latest at the time of submission of an application.

The following table provides some basic analytical tests for CGTPs.

**Table 3: Basic Analytical Tests for Cell and Gene Therapy Products**

Test	Cell Therapy Products (not limited to the listed tests)	Gene Therapy Products (not limited to the listed tests)	
		Viral	Nonviral and Antisense-Oligonucleotide
Identity of biological substance	Surface marker determination Species Morphology Genotypic/phenotypic markers Bioassay Biochemical marker	Restriction enzyme map PCR Immunoassay for expressed gene Sequencing and integrity of transgene	Restriction enzyme map PCR Immunoassay for expressed gene Sequencing and integrity of transgene
Dose	Viable cell number Enumeration of specific cell population Total DNA Total protein	Particle number Transducing units (DNA hybridization assay) Total protein HPLC assay using authenticated reference standard	Plasmid-DNA weight Formulated-complex weight HPLC or capillary electrophoresis assay using authenticated reference standard

Potency	Viable cell number (cells intended for structural repair) Bioassays: Colony-formation assay Function of expressed gene Induction of secondary effect (e.g., human leukocyte antigen (HLA) induction, secretion of cytokines, and up-regulation of surface marker)	Function of expressed gene (induction of secondary effect and other bioassays)	Function of expressed gene (induction of secondary effect and other bioassays)
Purity	Percentage of viable cells Percentage of transduced cells Percentage of cells with specific surface marker Percentage of differentiated cells Process contaminants (e.g., serum)	Residual host-cell DNA Process contaminants (e.g., serum and cesium chloride) Residual helper virus Optical density ratio Residual host-cell proteins Viral protein profile (HPLC assay for defective or immature particles) Residual RNA	Percentage of specific physical form (e.g., percentage supercoiled) Residual host-cell DNA Residual RNA Residual host-cell proteins Residual solvents Optical density ratio Process contaminants (e.g., cesium chloride and synthetic oligonucleotide by-products)
Safety	Mycoplasma Sterility Pyrogen and endotoxins Adventitious viruses Residual virus (for transplanted cells) Replication-competent vector virus, RCV (transfected cells)	General safety Mycoplasma Sterility Pyrogen and endotoxins Adventitious viruses RCV	Mycoplasma Sterility Pyrogen and endotoxins

Table adapted from the United States Pharmacopeia, USP 31-NF26

HPLC = high performance liquid chromatography

RCV = respiratory syncytial virus

## **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 and 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:

- Enumeration and viability
- Expression of phenotypic or genotypic markers
- Verification of morphology against visual reference standards
- Determination of population doublings, passage number, age of culture
- Assays of product- and process-related process impurities
- Monitoring of culture system parameters (e.g. % relative humidity, pH, glucose, etc.)
- Functional tests such as colony forming units (CFU) and expression of cell specific proteins
- Microbiological (sterility, endotoxin, mycoplasma) contaminants should be tested periodically to 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 9.3 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:

- Some release tests might not be feasible on the combined components of the active substance/ finished product for technical reasons

- 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.
- 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”
  - Ph. Eur. 5.1.6 “Alternative Methods for Control of Microbiological Quality”
  - Ph. Eur. 2.6.27 “Microbiological Control of Cellular Products”
- 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.

### **9.7 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 (July 1996)***.

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.

## **9.8 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 pharmaceuticals. 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.

## **9.9 PRODUCT TRACEABILITY**

A system allowing complete traceability of the patient as well as the product and its starting materials is essential to monitor the safety and efficacy of CGTPs. The system should allow full traceability from the donor to the recipient through anonymous coding systems. Manufacturers should establish their coding systems in a rational way, building from the coding system of the tissue establishment, and designing it to facilitate the tracing of the donation to the product and to the patient. Bar coding and peeling labelling systems could be suitable tools for the purpose of patient management.

## 9.10 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 granted (but are not limited) to the following items:

### **General information on active substance(s)**

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

### **Information related to the starting materials of active substance(s)**

- 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
- Cell bank system derived from continuous cell lines
  - Relevant requirements as to manufacturing and control of cell bank
- Viral safety evaluation & other adventitious agents

### **Information on the manufacturing process**

### **Information on quality control and process validation**

### **Characterisation of active substance**

**(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

**Pharmaceutical development of finished medicinal product:** Use of possible ancillary medical devices (bio-compatible polymers matrix, fibres, beads) in terms of bio-compatibility and durability

**Traceability:** Traceability of the product from the donor to the finished medicinal product

### **Specific requirements for xenogeneic cell therapy medicinal products**

## 10. PRE-CLINICAL STUDIES

The recommendations of the *ICH S6(R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals (Revision 1) (June 2011)* should be considered.

However, traditional, standardised approaches to preclinical safety 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)

- 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
- 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.

### Inherent risks of some CGTPs

- The fate of infused cells and tissue distribution profile of gene therapy products need to be determined.
- 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.

### Translation from bench to bedside use

- 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.
- 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

- A hybrid pharmacology-toxicology study in a model of disease/injury that more adequately reflect the clinical profile is recommended
- 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.

#### Combined CGTP

- For products intended to provide some mechanical support, biomechanical performance should be comprehensively assessed at multiple time points following product administration.
- 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.

#### Other safety considerations

- The need for reproductive studies is dependent on the CGTP and should be considered on a case-by-case basis
- 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
- 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.

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.

**For details on non-clinical studies, kindly refer to EMA Guideline on human cell-based medicinal products/ US FDA Preclinical Assessment of Investigational Cellular and Gene Therapy Products.**

## 11. 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:

- 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
- 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
- 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 CT products, 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, non-clinical 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.

An attempt should also be made 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 meaningful 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 CGTP 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, kindly refer to EMA's Guideline on human cell-based medicinal products.**

## 12. LABELLING REQUIREMENTS FOR IMMEDIATE AND OUTER PACKAGING

In addition to labelling requirements of biologic products in the *Drug Registration Guidance Document (DRGD), First Edition – January 2013*, 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 medicinal 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 medicinal products or waste derived from medicinal 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

- I. 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.

### 13. POST- AUTHORISATION REQUIREMENTS

#### Pharmacovigilance and Risk Management Plan (RMP)

- 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.
- 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.
- Traceability in the donor-product-recipient axis, or product-recipient axis for autologous products, is required in all circumstances.
- 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.
- As many of the CGTPs incorporate living organisms, 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 pre-registration clinical trials.
- 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.

- Periodic Safety Update Reports (PSURs) and their assessment reports should discuss on-going cumulative efficacy and safety data as well as safety data relating to donors and close contacts. Assessment of the effectiveness of the risk management system and the results of any newly finished studies should be regularly included in the PSUR and regular updates of the RMP. For CGTP-specific concerns in the RMP, please refer **Section 6.1 Safety Concerns in Guideline on safety & efficacy follow-up – Risk management of advanced therapy medicinal products (EMA, December 2008)**.
- The product registration holder (PRH) should inform the Drug Control Authority (DCA) of any steps which are to be taken with regards to safety concerns raised in the PSUR. A copy of the most updated relevant package insert/s should be submitted together with the PSUR. Any consequential variations (e.g. package insert changes) simultaneously with the PSUR at the time of its submission should also be submitted.
- The PRH must also inform the DCA within 3 calendar days of first knowledge by the registration holder, whether new evidence becomes available which may significantly impact on the benefit/risk assessment of a product or which would be sufficient to consider changes in the conditions of registration of the product.
- Additional pharmacovigilance data such as actual case reports, drug usage figures, the regulatory status of the product in other countries, independent pharmacoepidemiology studies, pre-clinical studies or significant product quality data may be requested by the Authority as the situation warrants. This must be submitted within a time period specified by the Authority.

#### **Adverse drug reaction reporting and Safety updates**

- In accordance with **Regulation 28 : Reporting adverse reaction under Control of Drugs and Cosmetics Regulations 1984, Sale of Drugs Act 1952 (amendment 2006)**, 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.
- The adverse drug reaction reporting should be in accordance with the **Malaysian Guidelines for the Reporting & Monitoring** (MOH Malaysia, March 2002).

- Product registration holders are required to monitor and report any product safety issues that arises locally or internationally to the NPCB and comply with all safety-related directives issued by the DCA.
- Regulatory action/s may be imposed if the PRH fails to inform the DCA of any serious adverse reactions upon receipt of such reports and safety updates.

### **Patient Registry for Class II Products**

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, June 2005)*** and the document entitled Guidance for Industry: ***Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. US FDA, March 2005*** may be referred and NPCB consulted.

## PART II. ADDITIONAL REQUIREMENTS ON XENOTRANSPLANTATION

Xenotransplantation refers to procedure that uses living, non-human animal cells, tissues or organs 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, tissues, or organs from a non-human animal source; or
- b. human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live non-human animal cells, tissues, or organs (e.g. extracorporeal perfusion)

[US FDA (2001) definition]

Examples of xenotransplantation products:

- 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.
- 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.
- Xenotransplantation products include those from transgenic or non-transgenic 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 CGTP regulation may apply to of 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 <i>Toxoplasma</i> spp., <i>Salmonella</i> spp.
	Experience with human allografts; transmission of HIV,CJD,HBV,HCV
Aggravating factors	Varying incubation periods and possible clinical latency of virus
	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 non-human 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:

- Appropriate clinical and scientific expertise of the xenotransplant research team and facility
- Stringent requirements regarding animal facilities, animal procurement and pre-transplantation animal source screening
- Risk minimisation precautions during all steps of production
- Thorough health surveillance program
- Very comprehensive informed consent and patient education process
- 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
- Xenotransplantation recipients to refrain from blood donation
- Biological specimens archived for public health investigations and for use by sponsor in conduct of surveillance of source animals and xenotransplantation recipients
- 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:

1. 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 (April, 2003)
2. US Public Health Services Guideline on Infectious Disease Issues in Xenotransplantation (January, 2001)
3. EMEA/CHMP/CPWP/83508/2009: Guideline on Xenogeneic Cell-Based Medicinal Products (December, 2009)

**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 guidances by US FDA and EMA and approval of products from these agencies may be a prerequisite for an application for registration of such products in Malaysia.

### **PART III. 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 vectors [viruses 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 GTP regulation includes:

- The addition and expression of a gene for therapeutic purposes
- The inoculation of nucleic acids for the purpose of developing therapeutic vaccines
- 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. Because gene therapy products are being developed around the world, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) via the ICH Gene Therapy Discussion Group are actively engaged in development of new guidelines. Three of these guidelines are available on the ICH website (<http://www.ich.org/consideration-documents.html>) - on Risk of Inadvertent Germ-line Integration of Gene Therapy vectors, Oncolytic Viruses, and Virus and Vector Shedding.

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 require 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 [US FDA, EMA, Health Canada, Swissmedic, TGA (Australia) and PMDA (Japan)].

## **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:

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

- Shedding studies to address excretion of the GTPs
- Biodistribution studies
- 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:

- Emergence of replication-competent vector
- Emergence of new strains

- Re-assortment of existing genomic sequences
- 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 a **Note for guidance on the quality, non-clinical and clinical aspects on gene therapy transfer medicinal products (April, 2001)**. Generally, the Note of Guidance provides general and specific considerations on:

- Development of genetics (also refer ICH Q5B)
  - suitability of the vector and delivery system
  - description and documentation of each element of the expression construct; scientific rationale based on their function and their inclusion in the expression vector
  - control and stability of gene expression
  - selection markers, etc.
- Manufacturing issues (ICH Q5A-5B-5D-5E)
  - the vector
  - cells (bacteria, cell lines, primary cells)
  - cell bank system (MCB/WCB)
  - viral seed lot system (MVS/WVS)
  - reagents (serum, growth factors, monoclonal antibodies)
  - TSE and viral safety
- Purification
  - suitability of the purification process to remove impurities (both process- and product-related impurities)
  - validation for the absence of extraneous viruses
- Characterisation and consistency (ICH Q6B)
  - identity, purity, potency
  - suitable tests: biological, immunological, biochemical
  - justification of the specifications
  - batch analysis on at least three consecutive batches
- Safety testing
  - sterility
  - pyrogens / endotoxins
  - mycoplasma

- freedom from adventitious agents
- *in vitro* and *in vivo* viral testing and species-specific viruses

## 14. ANNEX: ADDITIONAL REFERENCES ON CGTP REGULATION

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