**RESPONSE TO FEEDBACK RECEIVED FROM THE PUBLIC CONSULTATION ON THE PROPOSED REGULATION FOR CELL, TISSUE AND GENE THERAPY PRODUCTS UNDER THE HEALTH PRODUCTS ACT**

**FREQUENTLY ASKED QUESTIONS**

## DEFINITION

### 1. What are cell, tissue and gene therapy products (CTGTP)?

CTGTP refer to substances containing or consisting of

(i) Autologous or allogeneic human cells or tissues;

(ii) Viable animal cells or tissues; *or*

(iii) Recombinant nucleic acids (i.e. modified DNA or RNA as carriers of a therapeutic gene) that are administered for the diagnosis, treatment or prevention of any human disease or medical condition.

Examples: human demineralised bone, cell therapy products, stem cell derived products, tissue engineered products, gene therapy products, xenogeneic based products, regenerative medicine products.

### 2. What are the health products excluded from the CTGTP regulations?

The following types of products are excluded as they are covered by other legislations (i.e. Private Hospitals and Medical Clinics Act, Health Products Act or Human Biomedical Research Act (HBRA)):

| S/N | Product/ Purpose | Examples (for illustration purposes) |
|---|---|---|
| (i) | A recombinant vaccine for a preventive purpose | Dengue vaccine, COVID-19 vaccines – Regulated as Therapeutic Products under the Health Products (Therapeutic Products) Regulations. |
| (ii) | An *in-vitro* diagnostic product | Regulated as Medical Devices under the Health Products (Medical Devices) Regulations. |
| (iii) | Bone marrow, peripheral blood or umbilical or placental cord blood from a human that is minimally manipulated and intended for homologous use | Conventional bone marrow and cord blood transplant for treating haematological malignancies – Regulated under PHMCA Tissue Banking Services |
| (iv) | Cells and tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure. This includes removal and future implantation as a course of the | Clinical Practice:<br>➢ coronary artery bypass graft<br>➢ autologous skin grafting<br>➢ craniotomy or craniectomy with subsequent implantation of the |

| | | |
|---|---|---|
| | treatment, as the case may be, provided no other processing is performed. | bone flap to reverse the cranial defect |
| (v) | Organs and tissues that are minimally manipulated and intended for transplant | Conventional organ (Heart, Liver, Kidney, Cornea) and tissue (vascular tissue, trachea, skin) transplant - Regulated under PHMCA Tissue Banking Services |
| (vi) | Reproductive cells (sperm, eggs) and embryos intended for assisted reproduction | For In-vitro fertilisation procedures - Regulated under PHMCA Assisted Reproduction Services |
| (vii) | Whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders | Conventional blood transfusion – Regulated under PHMCA Blood Banking and Blood Transfusion Services |

## 3. How are CTGTP classified?

CTGTP are risk-stratified into two classes:

- Class 1 CTGTP (lower risk) have to satisfy ALL of the following criteria:
  (i) minimally manipulated, i.e. biological characteristics or functions of the cell or the structural properties of the tissue are not altered;
  (ii) intended for homologous use (performing same function and administered at the same anatomical site or histological environment in the recipient as in the donor); *and*
  (iii) not combined or used in conjunction with therapeutic products or medical devices.
- Class 2 CTGTP (moderate to higher risk) are those that are not Class 1 CTGTP and that includes viable animal cells and recombinant nucleic acids (reference to question 1).

Examples of Class 1 CTGTP:
Demineralised bone, amniotic membrane, bone grafts, skin, minimally manipulated cord blood and bone marrow.

Examples of Class 2 CTGTP:
Cultured chondrocytes, chimeric antigen receptor T cells, gene therapy products, tissue-engineered products, xenogeneic products (products containing viable animal cells/tissue).

## 4. Which processes are considered minimal manipulation?

The processes which do not alter the biological characteristics or functions of the cell, or the structural properties of the tissue are considered to be minimally manipulated. These processes include:

(i) cutting or sizing;
(ii) grinding;
(iii) shaping;
(iv) centrifugation;
(v) soaking in an antibiotic or antimicrobial solution;
(vi) sterilisation or irradiation;
(vii) cell separation, concentration or purification;
(viii) filtration;
(ix) lyophilisation;
(x) freezing;
(xi) cryopreservation;
(xii) vitrification; *or*
(xiii) other such process.

**5. Which processes are considered more than minimal manipulation?**

"More than minimal manipulation" means —

(a) in relation to the processing of a cell or tissue, any processing of the cell or tissue that results in the alteration of the biological characteristics or functions of the cell or structural properties of the tissue, as the case may be; *and*

(b) in relation to the processing of a gene, any processing of the gene.

Examples of processes that constitute more than minimal manipulation:
Cell expansion, cell activation (including genetic activation), gene manipulation and gene editing, cells grown on matrix, 3D bioprinting.

**6. What is homologous use?**

Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with a CTGTP that performs the same basic function or functions in the recipient as in the donor of the cells or tissues, and that the product is administered at the same anatomical or histological environment.

Examples of homologous use:

- Cord blood for haematopoietic reconstitution
- Demineralised bone matrix for orthopaedic application as filler for gaps or voids
- Amniotic membrane for wound covering
- Adipose tissue for breast reconstruction or augmentation procedures

Examples of non-homologous use:

- Cord blood for treatment of cerebral palsy
- Beta islets injected into the eyes for treatment of diabetes mellitus
- Bone marrow derived stem cells for cardiac repair

## REGISTRATION

### 7. What are the registration requirements for CTGTP?

- Product registration is not required for Class 1 CTGTP. Instead, the supplier will be required to notify HSA on the product and must receive HSA's written acceptance before it can be supplied. The supplier will also be required to ensure that the product is sourced from an accredited/licensed facility and that it is free from infectious agents.
- Class 2 CTGTP need to be assessed for its quality, safety and efficacy for its intended use and registered with HSA prior to supply in the local market.

### 8. What are the criteria to qualify for a conditional registration?

The conditional registration for Class 2 CTGTP allows an early market access for unmet medical needs with the necessary post-market safety and efficacy follow-ups.

The CTGTP need to meet all these criteria to be eligible for a conditional registration:

- intended to treat an unmet medical need*;
- product safety established in early clinical trials; *and*
- preliminary data shows meaningful evidence of therapeutic benefit (a clinically significant endpoint) versus other available therapies (standard of care)

The confirmatory studies data are required to be submitted within a prescribed timeline before obtaining full marketing approval. If not, the product will have to be withdrawn from the local market.

** An unmet medical need refers to:*

- *the absence of a treatment option; or/and*
- *the lack of safe and effective alternative treatments, and the product will allow a significant improvement in patient outcomes compared to available marketed products, as demonstrated by:*
    - *evidence of increased effectiveness in treatment, prevention, or diagnosis; or*
    - *elimination or substantial reduction of a treatment-limiting drug reaction*

**9. Is the submission of a Risk Management Plan (RMP) required as part of the CTGTP registration application?**

An RMP should be submitted as part of the product registration dossier for CTGTP.

The RMP documents to be submitted include:

- Singapore-Specific Annex (SSA)*
- Latest approved version of the European Union RMP and/or United States Risk Evaluation and Mitigation Strategies (if available)
- Proposed local RMP materials (e.g. draft educational materials, if any)

**The aim of the SSA is to outline important safety concerns and local pharmacovigilance and risk minimisation activities that the applicant is proposing to be put in place locally to monitor and mitigate the safety concerns identified. HSA has provided an SSA template under Annex I of the Guidance for Industry – Post-marketing Vigilance Requirements for Therapeutic Products and Cell, Tissue and Gene Therapy Products. Companies are recommended to follow the template when drafting the SSA.*

## Licensing

**10. What is the risk-based approach for dealer's handling CTGTP?**

Dealers are those persons involved in the activity of manufacture, import, and wholesale. Accordingly, dealer's licences refer to manufacturer's licence, importer's licence and wholesaler's licence.

The level of control for the activities of manufacture, import and supply is calibrated according to the degree of manipulation of the CTGTP.

<u>Minimally-manipulated CTGTP</u>

Manufacturers, importers and wholesalers handling minimally manipulated CTGTP will not require dealer's licences but will be required to notify HSA of their activities.

They will also be required to comply with the respective duties and obligations as specified in the CTGTP regulations such as duties to:

(a) Maintain records of manufacture;
(b) Maintain records of receipt and supply;
(c) Maintain system of traceability of the CTGTP and its starting and raw materials, including any substance that come into contact with the cells and tissue;
(d) Maintain records of defects and adverse effects; report defects and adverse effects;
(e) Notify the Authority concerning recall; *and*
(f) Notify the Authority before supply of Class 1 CTGTP.

More than minimally manipulated CTGTP

For manufacturers, importers and wholesalers handling more than minimally manipulated CTGTP, the respective dealer's licences of the engaged activity will apply.

Refer to the table below for the respective dealer's notification/licence and the applicable quality standards for dealers of CTGTP.

| **Degree of manipulation of CTGTP** | **Dealer Licence** | **Applicable quality standard for:** | | |
|---|---|---|---|---|
| | | **Manufacturer** | **Importer** | **Wholesaler** |
| CTGTP that is only minimally manipulated | No licence required (dealer's notification required) | GTP | GDP, GDP-MDS or ISO 13485 | GDP, GDP-MDS or ISO 13485 |
| CTGTP that is more than minimally manipulated | Respective licences apply | CTGTP GMP | GDP | GDP |

GTP: Good Tissue Practice Standard

GDP: Good Distribution Practice Standard

GDP-MDS: Good Distribution Practice Standard for Medical Devices

CTGTP GMP: HSA Guidelines on Good Manufacturing Practice (GMP) for CTGTP

**11. What activity will CTGTP Good Manufacturing Practice (GMP) requirements be applicable for?**

CTGTP GMP requirements will be applicable for the manufacture of CTGTP that are more than minimally manipulated.

**12. What are the GMP requirements for manufacturing CTGTP?**

HSA's Guidelines on Good Manufacturing Practice for CTGTP describe the GMP requirements for the manufacturing of CTGTP. It takes a risk-based approach in allowing flexibility to cater to changes as knowledge of the processes increases in tandem with the stage of clinical development of the product.

**13. When will existing CTGTP manufacturers (for products that involve more than minimal manipulation) be required to meet GMP standards?**

Existing CTGTP manufacturers will be given a 2-year grace period (from the implementation of the CTGTP framework) to meet the CTGTP GMP requirements and will be excepted from manufacturer's licence (ML) requirements during the said period. However, they need to comply with general duties of a manufacturer as specified in the CTGTP Regulations which include:

(a) Duty to maintain records of manufacture

(b) Duty to maintain records of receipt and supply

(c) Duty to maintain system of traceability of the CTGTP and its starting and raw materials, including any substance that come into contact with the cells and tissues

(d) Duty to maintain records of defects and adverse effects

(e) Duty to report defects and adverse effects

(f) Duty to notify Authority concerning recall

The existing CTGTP manufacturing facilities can continue to manufacture the products while preparing to obtain a ML or transfer its manufacturing operations to a GMP-certified facility.

**14. What are the record maintenance requirements/timelines for various activities?**

| **Type of Records** | **Timeline** | **Activity Role** |
|---|---|---|
| Records of Supply of Prescribed CTGTP (by retail sale of any CTGTP as prescribed by qualified practitioner) | Record of supply must be captured on the day on which the CTGTP is supplied or within 24 hours after that day. Record of supply must be kept 30 years after the expiry date of the CTGTP or any other shorter period as allowed by HSA. | Supplier (e.g. retail pharmacy, healthcare institution) |
| Records of Manufacture<br>(a) Records not related to traceability (e.g. batch processing record, results of release testing, deviations, procedures, records of qualification of premises and equipment, maintenance records, environmental monitoring records and change control records) | One year after the expiry of the CTGTP; or 5 years after the date of manufacture of the CTGTP, whichever is longer. | Manufacturer |
| (b) Records related to traceability of the CTGTP and its starting and raw materials, including any substance that comes into contact with the cells and tissues | At least 30 years after the expiry date of the CTGTP or any other shorter period that the Authority allows in a particular case. | |

| | | |
|---|---|---|
| Records of Receipt and Supply of CTGTP | At least 30 years after the expiry date of the CTGTP or any other shorter period that the Authority allows in a particular case. | Manufacturer<br>Importer<br>Wholesaler<br>Registrant |
| Records of Supply in relation to traceability system | At least 30 years after the expiry date of the CTGTP or any other shorter period that the Authority allows in a particular case. | Manufacturer<br>Importer<br>Supplier<br>Registrant |
| Records of defects and adverse effects | At least 2 years after the expiry of the CTGTP. | Manufacturer<br>Importer<br>Registrant |

**15. What are the qualifications of a Responsible Person who is required to be included in a dealer's licence?**

The holder of a dealer's licence must appoint one or more persons as a Responsible Person to be named in each licence. The Responsible Person is responsible for the activities conducted under the licence and should be contactable by the Authority at any time.

The Responsible Person must have the following qualities:

1. Adequate knowledge of the activities to be carried out
2. Relevant working experience

With reference to the Manufacturer's licence, the responsible person must have practical experience in the production supervision or in testing and checking of the quality of the CTGTP.

With reference to the Importers licence or wholesaler licence, the responsible person must have the practical experience in handling, storage and distribution of CTGTP to ensure quality of the CTGTP or any other practical experience that the HSA approves.

There is no professional certificate requirement for the responsible person for the dealer's licences.

**16. What is a control number?**

All CTGTP are required to be identified with an appropriate identification number/identifier. The identifier enables traceability of the CTGTP and is required to be maintained as part of the records of receipt and

supply, and records of defects and adverse effects. The identifier can be a serial number/batch number/control number/patient identifier/lot number.

## UNREGISTERED CTGTP

### 17. What are the conditions required for the import and supply of an unregistered Class 2 CTGTP?

Unregistered Class 2 CTGTP can be imported and supplied via Special Access Route (SAR) at the request of a qualified practitioner. Approval must be obtained for each consignment and must meet the following conditions:

- Product is approved by United States Food and Drug Administration (US FDA) or European Medicines Agency (EMA) and the product is from the same registered manufacturer as approved by US FDA or EMA;
- Results of the US FDA or EMA-approved release specifications or Certificate of Analysis is submitted upon import;
- The product is to be shipped and handled in accordance with the storage conditions specified in the US FDA or EMA approved package insert;
- The product should be used in accordance with the instructions provided in the US FDA or EMA approved package insert;
- Patient should be informed that the product is not registered with HSA and has not been evaluated for its quality, safety and efficacy, and prior consent should be obtained before its use;
- The therapy is approved by the respective healthcare institution's clinical ethics committee and/or the relevant professional board (e.g. tumour board for oncologic indications);
- Data should be collected on patient safety clinical outcomes and serious adverse events reported; *and*
- Patient records must be maintained for a period of 15 years (unless otherwise justified).

In addition to the above, the importer and supplier need to comply with the respective duties and obligations as specified in the CTGTP Regulations.

<u>For local clinical trial use</u>

Unregistered Class 2 CTGTP may be imported for local clinical trial use through a Clinical Research Material (CRM) Notification to HSA. The CRM notification may be made as part of the application for Clinical Trial Authorisation (CTA).

### 18. What are the conditions for the supply of an unregistered, locally manufactured Class 2 CTGTP?

Healthcare institutions (HCIs) manufacturing unregistered Class 2 CTGTP for supply to their patients must comply with the following:

- Patient should be informed that the product is not registered with HSA and has not been evaluated for its quality, safety and efficacy. Prior consent should be obtained from the patient before its use;
- Requirements stipulated by MOH on the use of in-house manufactured CTGTP (Click on the link for more information); *and*
- Respective duties and obligations for manufacturers and suppliers as specified in the CTGTP regulations, including duty to maintain records of manufacture, maintain records of receipt and supply, maintain system of traceability, maintain records of defects and adverse effects, report defects and adverse effects and to notify the Authority concerning recall.

In addition, if the CTGTP is more than minimally manipulated, the HCIs or contract manufacturers engaged by the HCIs must comply with the HSA Guidelines on Good Manufacturing Practice (GMP) for CTGTP and obtain a manufacturer's licence from HSA. Existing manufacturers are given a 2-year grace period from the implementation of the CTGTP regulations to comply with GMP requirements and are excepted from the manufacturer's licence during this period (please see Section on Licensing, question number 13).

## RECATEGORISATION OF EXISTING MEDICAL DEVICES CONTAINING HUMAN CELLS SUPPLIED UNDER MEDICAL DEVICE SPECIAL ACCESS ROUTE (SAR) TO CLASS 1 CTGTP

### 19. For current products that are imported under Medical Devices Special Access Route (MD SAR) that will be re-categorised to Class I CTGTP, what are the additional requirements that importers need to meet?

Medical devices containing human cells and tissues (e.g. human bone graft) that are supplied through MD SAR will be re-categorised as Class 1 CTGTP. These products will be included in the Class 1 CTGTP Register when the CTGTP Regulations are implemented.

The requirements of the re-categorised products are as follows:

| Role | Not Required | Required |
|---|---|---|
| Dealers (Manufacturer, Importer, Wholesaler) | Dealer Licences | • New dealers to notify HSA<br>• All dealers to comply with duties and obligations<br>[Documents required will be the same as the current MD SAR application.] |
| Suppliers (Manufacturer, Importer, Wholesaler) | Product Registration | • Notify HSA of the product when<br>  ○ the MD SAR approval expires; or<br>  ○ there is a new accreditation certificate; or<br>  ○ when you intend to supply a new product<br>• Obtain HSA's acknowledgement prior to supply |

| | | |
|---|---|---|
| | | [Documents required will be the same as the current MD SAR application.] |

The document requirements are as follows (same as per current MD SAR application):

- Certified true copy of a valid certificate of accreditation (e.g. AABB, AATB, FACT, CAP)
- Evidence demonstrating that the establishment is registered with local regulatory agency (e.g. US FDA establishment registration and listing for HCT/Ps, Health Canada CTO registration certificate, UK Human Tissue Authority)
- Product release specifications or Certificate of Analysis
- Product label and package insert
- Product shelf-life and container closure (packaging) information

New dealers (manufacturer, importer and wholesaler) that handle CTGTP that are only minimally manipulated are required to notify HSA. No acknowledgment is required from HSA and following notification such dealers will be deemed known manufacturer, known importer and known wholesaler.

Prior to supply, all new Class 1 CTGTP shall be notified to HSA and can only be supplied following written acceptance of notice from HSA. Since Class 1 CTGTP are not registered, the SAR route is not applicable.

## CLINICAL TRIALS OF CTGTP

### 20. How are CTGTP clinical trials (CT) regulated?

A risk-based approach is applied for the regulation of clinical trials of CTGTPs.

- Higher risk Class 2 CTGTP clinical trials will be regulated under the existing Clinical Trial Authorisation (CTA) - Clinical Trial Notification (CTN) framework under the Health Products (Clinical Trials) Regulations.
- Lower risk Class 1 CTGTP clinical trials will not be regulated by HSA. Such trials may proceed with Institutional Review Board (IRB) approval and must comply with the requirements under the HBRA and its Regulations.

### 21. What are the requirements for Clinical Research Materials for CTGTP?

To facilitate access to clinical research material that is a CTGTP for the purpose of use in a clinical trial or clinical research, dealer licences for the manufacture, import and wholesale supply, and product registration are not required. This is provided a CRM notification is made before:

- Import of the clinical research material for local clinical research use
- Supply by the local manufacturer of the clinical research material for local clinical research use.

CRM dealers (manufacturers, importers, wholesalers, suppliers including sponsors and investigators) are required to comply with the duties and obligations as specified in the Health Products (Clinical Research Materials) Regulations. These duties include but are not limited to restricting the supply of the clinical research material for use in a clinical trial or clinical research, ensuring the CRM is appropriately labelled, keeping appropriate records of manufacture, receipt and supply, and safety and product defect reporting to HSA within stipulated timelines.

## REPORTING OF PRODUCT DEFECTS

### 22. What are the reporting timelines for defects?

Upon becoming aware of a product defect, every manufacturer, importer, supplier or registrant of a CTGTP product must, upon becoming aware of any defect in the CTGTP, report the defect to HSA in accordance to the following timelines:

a) if the defect represents a serious threat to persons or public health, within 48 hours; or
b) in all other cases, within 15 days.

If there is a critical defect which poses a safety risk to public, prompt measures should be taken to minimise the risk (including market actions). If it is genuinely not possible to obtain the information in a timely manner, the HSA should be consulted, to agree on timelines and required actions, if any. If the information required for reporting is available, the company should not delay the submission of the product defect report while conducting the root cause investigation.

**Question will be posted after the exemption order is finalised by AGC**

## REQUIREMENTS OF OUT OF SPECIFICATION CLASS 2 CTGTP

### 23. Supply of a CTGTP that is Out of Specifications (OOS)

In exceptional circumstances, the supply of a CTGTP that is OOS (does not meet some of the release specifications) may be considered to avoid an immediate significant hazard to the patient, such as when the patient is in a clinically dire situation and there are no alternative treatment options available.

Such OOS products may fall within the definition of an unwholesome health product under the Health Products Act [section 2, (2)(d)(i) and (ii)] and will require an exemption from the prohibition of the manufacture, import and supply of unwholesome health product, to enable supply under such exceptional circumstances.

Exemptions from sections 12(5)(c), 13(5)(d) and 16(1)(d) of the HPA for the manufacture, import and supply, as the case may be, are required for a CTGTP that is more than minimally manipulated and is an autologous CTGTP containing viable human cells or tissues, that does not meet the pre-defined product specifications under specified circumstances.

The exemptions from the manufacture, import and supply of CTGTP, which would otherwise be considered unwholesome must comply with the following conditions:

(i) Administration of the product is necessary to avoid an immediate significant hazard to the patient, where after taking into account the alternative treatment options, the risk of failure to treat would be higher than that associated with administering the OOS product to the patient, or in the case of a clinical research material that is a CTGTP, the potential benefits outweigh the potential risks of administering the OOS product to the trial participant;

(ii) The manufacturer should provide a risk assessment to the qualified practitioner treating the patient;

(iii) Supply of the product is requested by the qualified practitioner treating the patient, after having considered the specific condition of the patient and the evaluation of risks provided by the manufacturer;

(iv) Professional consensus by the institution's professional board, or written endorsement by an independent specialist, supporting the use of the product for the patient's condition is provided, or in the case of a clinical research material that is a CTGTP, the institutional review board is notified of the use of the OOS CTGTP in the trial participant in accordance with the requirements of the board;

(v) Patient or legal representative (where applicable) is informed of the OOS CTGTP and its associated risks, and gives written informed consent to receiving treatment with the product;

(vi) The manufacturer / registrant / sponsor of a regulated clinical trial (as applicable) is required to notify HSA of supply of the product within 48 hours after the product has been administered to a patient.