Guidance for Cell and Tissue Products

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Department of Health

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Enquiries

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Chapter 1 Background

1.1 In October 2012, the Government established the Steering Committee on Review of Regulation of Private Healthcare Facilities to conduct a review of the regulatory regime for private healthcare facilities in Hong Kong. The aim of the review is to strengthen regulatory control of private healthcare facilities in order to safeguard public health. A specific working group was set up under the Steering Committee to examine the regulatory control of premises processing health products for advanced therapies. In its final report[1], the Working Group recommended that all processes on cells and tissues for human application including donation, procurement, testing, processing, preservation, storage and distribution should be subject to regulation. Cells and tissues for human application should be regulated according to their risks to human health as determined by (1) intended use; and (ii) extent of manipulation[1]. As such, cells and tissues which have been substantially manipulated or are intended for non-homologous use are considered as having higher risk, and would be subject to more stringent regulation than those which have received minimal manipulation and intended for homologous use.

1.2 In 2017, the Government set up a Task Force on Regulation of Advanced Therapeutic Products in Hong Kong to advise the Government in formulating the regulatory framework for cell and tissue-based products. The Terms of Reference and Membership of the Task Force can be found in **Annex A**. The public consultation which was conducted in mid-2018 proposed to include the definition of advanced therapy products (ATPs) under the definition of

pharmaceutical products in the Pharmacy and Poisons Ordinance, Cap. 138 ("PPO"). Requirements on product registration, licensing of manufacturers and distributors, import/export control, approval for clinical trials, labelling, record keeping and adverse event reporting would apply for these products. There was broad support for the proposed regulatory framework for ATPs set out in the consultation document[2]. Further details of the consultation exercise can be found at: http://www.advancedtherapyinfo.gov.hk/cbb/en/level.html. The Pharmacy and Poisons (Amendment) Bill 2019 (the Bill) was introduced into the Legislative Council to amend the "PPO" (Cap. 138). The Bill was passed on 17 July 2020.

1.3 To address the quality and safety of cell and tissue products other than ATPs, the Department of Health adopts a whole-process approach to inform the industry and stakeholders with the current guidance. Extensive reference was made to overseas regulations, such as the relevant European Union (EU) directives and the Good Tissue Practice of the United States, in developing the guidance.

Chapter 2 Scope of the Guidance

2.1 For the purpose of the guidance, cell and tissue products refer to ***human cells or tissues subject to minimal manipulation and intended for homologous use***[1]. They are generally regarded as imposing lower health risk as compared to ATPs, which have been subject to substantial manipulation or are intended for non-homologous use.

2.2 Certain cells and tissues are regulated by existing legislations such as Cap. 465 the Human Organ Transplant Ordinance (HOTO) and Cap. 561 the Human Reproductive Technology Ordinance. Please refer to **Annex B** for more information. For the cells and tissues that are regulated under the ordinances, the relevant provisions of the ordinances shall be fully complied with. Please refer to Hong Kong e-Legislation for the provisions of the ordinances at http://www.elegislation.gov.hk.

Chapter 3 Aim of the Guidance

3.1 The aim of the guidance is to provide the industry and stakeholders, including organisations involved in donor screening, testing, procurement, processing, storage, labelling, and distribution of cell and tissue products, with minimum requirements to prevent disease transmission and to ensure the quality and safety in their handling and utilization.

3.2 Stakeholders are encouraged to make reference to overseas relevant good practice guides/guidelines such as the *Guide to the quality and safety of tissues and cells for human application* published by the European Directorate for the Quality of Medicines & Healthcare of the Council of Europe, or the *Current Good Tissue Practice* published by the US Food and Drug Administration. These guides/guidelines provide specific requirements for different tissues in addition to general principles in handling human cells and tissues. Compliance with good practice guides/guidelines help to ensure the performance of staff and the quality of the products. Please refer to **Annex C** for a list of overseas guides/guidelines to make reference to.

3.3 Stakeholders are also encouraged to seek continuous accreditation from relevant competent bodies. Accreditation involves regular evaluation and on-site inspection on the compliance and is usually process or program-specific. Obtaining accreditation indicates that the industry and its organisations are dedicated to excellence in service. It is also a recognition, by competent bodies operating under a standard accreditation process, of the capability of the facility

to perform specific activities. Please refer to **Annex D** for a list of accreditation organisations.

Chapter 4 The Guidance

4.1 Quality Management System

i. Tissue establishment must implement and maintain a quality management system (QMS) which includes, as a minimum requirement, the following documentation: standard operating procedures (SOP), guidelines, training and reference materials, reporting forms, donor records and information on the final destination of cells and tissues.

Organisation and Management

ii. A responsible person having relevant qualifications and responsibilities must be appointed to oversee the running of the QMS.

iii. An organizational chart must be present which clearly defines accountability and reporting relationships.

iv. Repeated risk assessment should be performed and risk mitigation strategies should be developed.

v. A documentation system must be in place for determining whether cells and tissues can meet appropriate specifications for quality and safety for release.

vi. A documentation system must be in place that ensures the identification of every unit of cells or tissues at all stages of activities.

Quality Review

vii. An audit system must be in place to ensure compliance with the SOP and the regulatory requirements. Deviations must be investigated and documented, including findings and possible corrective and preventive actions.

viii. Any new or significant changes to the existing processing and storage procedures must be validated and documented before they are implemented.

ix. The processing and storage procedures must undergo regular evaluation to ensure that they continue to fulfill the intended purposes and achieve the intended results.

x. Deviations from required standards must lead to documented investigations. All affected cells and tissues must be identified and accounted for. The fate of non-conforming cells and tissues must be decided in accordance with written procedures supervised by the responsible person and recorded.

xi. Corrective actions for deviation from required standards must be documented and initiated in a timely and effective manner. Preventive actions should be assessed for effectiveness.

xii. A process should be in place for the review of the performance of QMS to ensure continuous and systematic improvement.

4.2 Personnel

i. There must be sufficient qualified and competent staff for carrying out the activities of the tissue establishment.

ii. The tissue establishment must have access to a nominated registered medical practitioner to advise on and oversee the establishment's medical activities.

iii. Clear documentation of job description and assigned duties of the staff must be available.

iv. Staff training programmes should be in place and training records must be maintained. Personnel involved in the donation, procurement, testing, processing, preservation, storage and distribution of cells and tissues should have timely and relevant training.

4.3 Equipment and Materials

i. Equipment and technical devices must be identified, validated, regularly inspected and preventively maintained in accordance with manufacturers' instructions. New and repaired equipment must be validated before use.

ii. Maintenance, servicing, cleaning, disinfection, sanitation and calibration of equipment must be performed regularly and recorded accordingly.

iii. Specifications of reagents and materials must be documented.

iv. Inventory records and certificate of compliance for every lot of materials must be kept. Materials must not be used after their expiry date.

v. In the event of failure, SOPs with details of actions to be taken must be available.

4.4 Premises and Facilities

i. The tissue establishment should be of suitable size and location, and must have suitable facilities for carrying out the handling of cell and tissue products.

ii. A controlled environment with specified air quality, cleanliness, temperature and humidity appropriate for the type of cell and tissue must be present for handling of cell and tissue products. A validated cleaning protocol for processing environments must be present to minimise the risk of contamination.

iii. Separate storage facilities must be provided to distinguish cells and tissues that are rejected, in quarantine, or ready to release, to prevent mix up and cross contamination.

iv. Parameters, such as temperature, humidity and air quality, must be controlled, monitored, and recorded to demonstrate compliance with the specified storage conditions.

v. Written policies and procedures must be present for controlled access, cleaning and maintenance, waste disposal and re-provision of service in emergency situation.

4.5 Documentation

i. There must be a system in place that results in clearly defined and effective documentation, correct registers and authorized SOPs. Documents must be regularly reviewed. The system must ensure that work performed is standardized and all steps are traceable.

ii. All changes to documents must be reviewed, dated, approved, documented and implemented promptly by authorized personnel.

iii. Documentation must be clear and indelible, reliable, properly maintained and easily retrieved.

iv. Access to registers and data must be restricted to persons authorized by the responsible persons.

4.6 Donation

i. Living donations for transplant must comply with Cap. 465 HOTO. The donor must have given his consent to the removal of the tissues for the purpose of producing the product without coercion or the offer of inducement. No payment must have been made, or is intended to be made to that donor for his supplying the tissues. The product for

transplant purpose must be safe and has no adverse impact on public health, and all applicable laws of the place where the tissues were obtained or processed have been complied with in obtaining and processing the tissues.

ii. Import of any tissues or organs intended for transplant must comply with the requirement specified in Cap. 465 HOTO and Cap. 599 Prevention and Control of Disease Ordinance. Consent must be obtained before the procurement of the tissues or organs.

iii. Deceased donor donations must comply with Cap. 278 Medical (Therapy, Education and Research) Ordinance. The donor must have given his prior consent to the removal of the tissues after his death for therapeutic purposes and for purposes of research; otherwise, certain conditions must be met, e.g. written consent of the registered next of kin of the deceased has been obtained.

iv. Selection criteria for allogeneic donors must be present, based on an analysis of the risk related to the application of the specific cells or tissues. Some exclusion criteria include: unknown cause of death, unknown disease aetiology, malignancy, infectious disease, intoxication, deferred for blood donation for unknown reason, etc.

v. Indicators of these risks must be identified by physical examination, review of medical and behavioural history, biological testing, post mortem examination (for deceased donors) and any other appropriate investigation.

4.7 Testing

i. To reduce risk of infectious diseases, minimum tests to be carried out on allogeneic donor cells or tissues include:

(a) Human immunodeficiency virus antibody (HIV I and II)

(b) Hepatitis B virus surface antigen (HBsAg)

(c) Hepatitis C virus antibody (HCV)

(d) Syphilis

ii. For autologous donors, the same minimum set of testing requirements must apply but positive test results will not necessarily prevent the cells or tissues from being processed or stored, if appropriate isolation and storage facilities are available to ensure no risk of cross contamination.

iii. Additional tests may be required according to the tissue type to be procured and the intended use. Guidelines from relevant professional bodies should be observed.

iv. Tests must be performed by qualified, accredited or licensed laboratories using approved and validated tests.

4.8 Procurement

For Cells and Tissues

i. The consent and identity of the donor must be verified.

ii. For allogeneic donation, the donor must be evaluated before procurement which include examination of records and a physical examination when justified.

iii. Procurement procedures must be appropriate for the type of donor and the type of cell or tissue donated.

iv. Procurement procedures must protect the property of the cells or tissues that are required for the clinical use and at the same time minimise the risk of microbiological contamination during the process.

v. The procurement area for deceased donation must have restricted access. A local sterile field using sterile drapes must be used. Staff conducting procurement must be clothed appropriately for the type of procurement.

vi. There must be procedures in place, such as infection control, surgical and anaesthetic risk assessments, to protect the health and safety of the living donor.

vii. A documentation system must be in place to contain donor records which include a unique identification number for the donor, and procurement reports which include the details of the procurement procedures and persons involved.

For Reagents and Materials

viii. Reagents and materials must meet the documented requirements and specifications.

ix. Sterile single-use materials, such as drapes and gloves, must be used for cell and tissue procurement.

x. A system must be in place that allows traceability and tracking of reagents and materials to each cell- or tissue-procurement event and to the donor.

4.9 Reception

i. On arrival of cells and tissues at tissue establishment, there must be documented verification that the batch of cell or tissue, including the transport conditions, packaging, labelling and associated documentation and samples, meet the requirements of the establishment to ensure the quality and safety of cells and tissues. The acceptance or rejection of received cells and tissues must be documented.

ii. Cells and tissues must be quarantined and stored in a defined and separated location and under appropriate conditions until they have been verified as conforming to requirements.

iii. Tissue establishments must have a documented policy and specification against which the received cells and tissues are verified. These must include the technical requirements and other criteria considered to be essential for the maintenance of acceptable quality.

iv. The packing, cells and tissues received and any accompanying samples should all be examined to ensure that they have not been damaged or tampered with during transit.

4.10 Processing

i. Cells and tissues should be appropriately processed and preserved for clinical use. Processing must not render cells and tissues clinically ineffective and must avoid contamination and prevent the transmission of communicable diseases.

ii. Processing must be validated, that is, to ensure it consistently meets predetermined specification. Staff must be able to carry out the processes consistently.

iii. SOPs must be in place to ensure all processes, including those for handling the cells and tissues to be discarded, are conducted in accordance.

iv. Any microbial inactivation procedures or terminal sterilisation procedures applied to the cells and tissues must be specified, documented and validated.

v. Procedures discarding cells and tissues must prevent the contamination of other donations and products, the processing environment or personnel.

vi. Reagents used in processing and preservation should be of an appropriate grade for their intended use and be sterile, if applicable. They should be used in a manner consistent with the instructions provided by the manufacturer.

vii. Entry of personnel and materials to the processing facilities, transit and exit of personnel and materials through the processing area and the rules of use and clothing to be worn in them should be established in order to minimize the risk of contamination of cells and tissues.

4.11 Storage

i. Tissue establishments must ensure that all storage processes are carried out under controlled conditions. Storage must not render cells or tissues clinically ineffective and must avoid contamination and prevent the transmission of communicable diseases and mix-up.

ii. Tissue establishments must establish and apply procedures for the control of storage areas, in order to prevent any situations arising that might adversely affect the functioning or integrity of cells and tissues.

iii. Regular monitoring and recording of temperature, together with suitable alarm systems, must be employed on all incubators, storage refrigerators, freezers and liquid nitrogen tanks.

iv. Maximum storage time must be specified for cells and tissues. Expiry date for each type of storage condition must be indicated.

v. The storage requirements must be appropriate to each tissue type and its intended application.

vi. All procedures associated with storage of cells and tissues must be documented in the SOP.

4.12 Labelling for Final Distribution

i. An internationally recognized system for coding and labelling of human cells and tissues, e.g. ISBT 128 maintained by the International Council for Commonality in Blood Banking Automation, **ICCBBA**, must be adopted. Or else, there must be a mechanism in place to demonstrate how the uniqueness in identification of the donors and traceability are maintained.

ii. All containers for packaging cells and tissues must be clearly labelled. The label must include:

(a) Type of cell or tissue
(b) Unique identification number of cells and tissues
(c) Identification of tissue establishment
(d) Expiry date
(e) Hazard warning
(f) Specification of transport and storage conditions
(g) If the product is for autologous use only, this must be specified “for autologous use only” and the donor/recipient must be identified

iii. In addition to the information stated in (ii) above, the label or the accompanying documentation must include, but not limited to the following additional information:

(a) Description and, if relevant, dimensions of cell and tissue products

(b) Morphology and functional data where relevant

(c) Date of distribution of cells and tissues

(d) Storage instructions

(e) Instructions for opening containers, package, and any required reconstitution

(f) Presence of potential harmful residues (e.g. antibiotics, ethylene oxide, etc.)

iv. The labels must be waterproof, scratch resistant and have good adhesive property. Message must be clear and legible.

4.13 Distribution

i. A comprehensive record review, including relevant medical records, procurement records, test results and processing records, must be performed prior to release to ensure the quality and safety of cells and tissues to be distributed.

ii. There must be a system of inventory hold for cells and tissues to ensure that they cannot be released until all requirements have been satisfied. Cells and tissues must be quarantined at any stage when their release could affect the quality or safety.

iii. Transport, packaging and delivery of cells and tissues must be appropriate for the type to ensure the quality and safety.

iv. Distribution to end users must ensure traceability is maintained and that serious adverse events or reactions are reported back to the tissue establishment.

v. Documented agreement must be present if there is a third party involved in the transportation and distribution to ensure the required conditions are maintained.

vi. A recall mechanism which include description of responsibilities and actions to be taken must be in place.

4.14 Traceability

i. Cells and tissues must be traceable through documentation from procurement to human application and vice versa. This traceability must also apply to all relevant data relating to products, reagents and materials coming into contact with these cells and tissues. Risks associated with clinical use of cells and tissues include donor transmitted infections, malignancies and genetic conditions.

ii. A donor identification code unique to each donation and to each of the products derived from it must be implemented.

iii. Tissue establishments must keep the data necessary to ensure traceability at all stages. Data required for full traceability should be kept for at least 30 years after clinical use. Data storage may also be in electronic form.

4.15 Serious Adverse Reactions and Events

i. A system must be in place for detecting, reporting, investigating and evaluating adverse reactions or events.

ii. A communication channel is needed for the reporting of adverse reactions or events, e.g. between tissue establishments, with clinicians or end users.

iii. Immediate actions must be taken to limit the damage, e.g. identification of donor and other recipients, recall of products, etc.

iv. Tissue establishment must ensure that an accurate, rapid and verifiable procedure is in place which will enable it to recall from distribution any product and reagent which may be related to an adverse event or reaction.

v. An investigation with root cause analysis must be undertaken in a timely manner. Corrective and prevention actions must be implemented.

vi. Any incidents that occur during clinical application and any adverse reactions and events must be documented and reviewed.

4.16 Third Party Agreement

i. If any of the activities of the tissue establishment are carried out by an external party, there must be a written agreement which specifies responsibilities between the third party and the tissue establishment. Accreditation documents and independent audit reports should be in place.

ii. A third party that is able to meet the standards set out in the guidance must be sought.

References

1. Report of the Working Group on Regulation of the Premises Processing Health Products for Advanced Therapies. (https://www.fhb.gov.hk/download/press_and_publications/otherinfo/180500_phf/Report_on_WG3_of_Regulation_of_Premises_Advanced_Therapies_2014_e.pdf)

2. Consultation Report – Regulation of Advanced Therapy Products. (http://www.advancedtherapyinfo.gov.hk/cbb/en/doc/ATP_Consultation_Report_en.pdf)

Glossary/ Definitions

For the purpose of the guidance, **high risk and lower risk cells and tissues** are defined as follows:

***Advanced therapy products**: Any of the following products that is for human use – (a) a gene therapy product; (b) a somatic cell therapy product; (c) a tissue engineered product. They are considered as high risk.

***Gene therapy product:**

Gene therapy product –

(a) means a product –

(1) that contains an active substance containing or consisting of a recombinant nucleic acid that may be used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence; and

(2) the therapeutic, prophylactic or diagnostic effect of which relates directly to –

i. the recombinant nucleic acid sequence it contains; or

ii. the product of genetic expression of that sequence; but

(b) does not include a vaccine against an infectious disease.

***Somatic cell therapy product**:

Somatic cell therapy product

(a) means a product that –

(1) contains or consists of any of the following cells or tissues—

i. cells or tissues that have been subject to substantial manipulation so that their biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered;

ii. cells or tissues that are not intended to be used for the same essential functions in their recipient as in their donor; and

(2) is presented as having properties for, or may be used in or administered to human beings with a view to –

i. treating, preventing or diagnosing a disease; or

ii. restoring, correcting or modifying physiological functions,

through the pharmacological, immunological or metabolic action of those cells or tissues.

***Tissue engineered product:**

Tissue engineered product –

(a) means a product that –

(1) contains or consists of any of the following cells or tissues –

i. cells or tissues that have been subject to substantial manipulation so that their biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement have been altered;

ii. cells or tissues that are not intended to be used for the same essential functions in their recipient as in their donor; and

(2) is presented as having properties for, or may be used in or administered to human beings with a view to, regenerating, repairing or replacing a human tissue; but

(b) does not include a product that –

(1) contains or consists of exclusively non-viable human or animal cells or tissues; and

(2) does not act principally by pharmacological, immunological or metabolic action.

***Cell and tissue products**: Human cells or tissues subject to minimal manipulation and intended for homologous use are usually considered as of lower risk.

Definition of **other general terms** in the guidance:

Allogeneic use: Cells or tissues removed from one person and applied to another.

Autologous use: Cells or tissues removed from and applied to the same person.

Cells: Individual human cells or a collection of human cells when not bound by any form of connective tissue, including cell lines grown outside the human body.

Distribution: Transportation and delivery of cells and tissues intended for human application. A person who, from any premises, controls the provision of services for transporting cells and tissues is to be taken to distribute cells and tissues from those premises.

Donation: Donating human cells, tissues or organs intended for human application.

Donor: The person from whom cells, tissues or organ(s) is, or is intended to be removed for human application.

Homologous Use: The repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with a product that performs the same essential functions in the recipient as in the donor. This definition is related to the use of the product independent of whether the recipient is the same as the donor (autologous) or different from the donor (allogeneic).

Minimal manipulation: Taken into account the methodological complexity of advanced therapy products and in order to reduce the possible interpretations, minimal manipulation of cells and tissues include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, and vitrification.

Organ: Any human bodily part which –

(a) consists of a structured arrangement of tissues; and

(b) if wholly removed, cannot be regenerated by the body.

Preservation: The use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells and tissues.

Processing: All operations involved in preparation, manipulation, preservation and packaging of cells and tissues intended for human application.

Procurement: A process by which cells and tissues, as well as reagents and materials, are made available.

Quality management system (QMS): A systematic approach addressing all stages of activities to ensure the quality and safety of cells and tissues, and that they are fit for their intended use. It should be tailored for different cell and tissue products.

Quarantine: The status of retrieved or procured cells and tissues, whilst awaiting a decision on their acceptance or rejection.

Recipient: The person into whom cells, tissues or organ(s) of the donor is or intended to be transplanted.

Serious adverse events: Any untoward occurrence which may be associated with the testing, procurement, processing, storage or distribution of cells or tissues intended for human application and in which might lead to the transmission of a communicable disease, to death or life threatening, disabling or incapacitating conditions, or might result in, or prolong, hospitalisation or morbidity.

Serious adverse reaction: An unintended response, including a communicable disease, in a donor or a recipient which may be associated with the procurement or human application of the cells or tissues and which is fatal, life threatening, disabling, incapacitating or which results in, or prolongs, hospitalisation or morbidity.

Standard Operating Procedure (SOP): Written instructions describing the steps in a specific process, including the materials and methods to be used and the expected end product.

Storage: Maintaining cells and tissues, whether by preservation or in any other way, under appropriate controlled conditions until distribution.

Substantial manipulation: Substantial manipulation, in relation to cells or tissues, does not include the manipulation processes set out in the definition of minimal manipulation.

Tissue establishment: A tissue bank or a unit of a hospital or another body where activities of processing, preservation, storage, distribution or import/export are undertaken. It may also be responsible for procurement or testing of cells and tissues.

Tissue or Tissues: All constituent parts of the human body formed by cells, but does not include organs.

Traceability: The ability to locate and identify the cells and tissues during any step from procurement through processing, testing and storage, to distribution to the recipient or disposal, which also implies the ability to identify the donor and the tissue establishment or the manufacturing facility receiving, processing or storing the cells and tissues, and the ability to identify the recipients at the medical facility applying the cells and tissues to the recipients. Traceability also covers the ability to locate and identify all relevant data relating to products, reagents and materials coming into contact with these cells and tissues.

Validation: Establishing documented evidence that provides a high degree of assurance that a specific process, SOP, piece of equipment or environment will consistently produce a product meeting the predetermined specifications and quality attributes; a process is validated to evaluate the performance of a system with regard to its effectiveness based on intended use.

Annex A

Task Force on Regulation of Advanced Therapeutic Products in Hong Kong

Terms of Reference and Membership

Terms of Reference

- To examine and to advise the Government on setting up a regulatory regime for cell and tissue-based therapy and health products for advanced therapies in Hong Kong;
- To advise the Government on the approach for stakeholder consultation and engagement; and
- To advise the Government on the preparation of good practice guidelines for handling cells and tissues for human application.

Membership

Chairman

Professor LAU Chak Sing

Members

Professor Barbara CHAN

Professor Godfrey CHAN

Dr LEE Cheuk Kwong

Ms Kim LEE

Professor Kathy LUI

Dr Cecilia PANG

Professor POON Wai Sang

Annex B

Existing Legislation

Certain tissue products are already regulated under Cap. 465 the Human Organ Transplant Ordinance (HOTO). The HOTO aims to prohibit commercial dealings in human organs intended for transplanting, to restrict the transplanting of human organs between living persons and the transplanting of imported human organs, and for supplementary purposes connected with those matters.

Certain commercial products made from human tissues (such as skin and bone derived products) are available for transplanting purposes, but these products fall within the definition of "organ" under HOTO. To allow registered medical practitioners and registered dentists in Hong Kong to use these products for transplant, amendment has been made to the HOTO to provide for the Director of Health a mechanism to exempt these products from the provision of commercial dealings and other sections of the HOTO as appropriate. However, the principles enshrined in the HOTO that donation of human tissues and organs for making of these products is on a voluntary basis are upheld.

A product which falls within the definition of “organ” and has been subjected to “processing” as stipulated in the HOTO is regarded as “regulated product”. The Director of Health may, on application, exempt a regulated product from the application of the whole or any part(s) of the HOTO if –

(a) the product for transplant purpose is safe and has no adverse impact on public health;

(b) the donor of the tissues concerned has given his consent to the

removal of the tissues for the purpose of producing the product without coercion or the offer of inducement; and

(c) no payment has been made or is intended to be made to that donor.

For more information, please refer to the following URL: https://www.dh.gov.hk/english/useful/hot_exemption.html.

On the other hand, the handling, storing or disposing of gametes or embryos used or intended to be used in connection with a reproductive technology procedure or embryo research is regulated by Cap. 561 the Human Reproductive Technology Ordinance. Cap. 561 aims to regulate reproductive technology procedures, and the use, for research and other purposes, of embryos and gametes; to confine the provision of reproductive technology procedures to infertile couples subject to any express provision to the contrary in any code; to regulate surrogacy arrangements; to establish a Council on Human Reproductive Technology; and to provide for matters incidental thereto or connected therewith.

For more information, please refer to the following URL: http://www.chrt.org.hk.

Annex C

List of Overseas Guides/ Guidelines for Reference

The ***EU Directive 2004/23/EC*** (https://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1570776135704&uri=CELEX:32004L0023) sets out the legal framework defining the quality and safety standards for cells and tissues. It covers all steps in the transplant process from donation, procurement, testing, processing, preservation, storage and distribution. This basic act is supplemented by implementing EU directives (Directive 2006/17/EC, 2006/86/EC, 2015/565 and 2015/566) which concern additional technical requirements and procedures in the transplant process.

The ***Guide to the quality and safety of tissues and cells for human application*** (https://www.edqm.eu/en/organs-tissues-and-cells-technical-guides) is regularly reviewed and updated by the Council of Europe and provides technical requirements on the transplantation of human cells and tissues. The Guide aims to provide sound information and guidance to optimize the quality and minimise the risk of the procedures of donation, banking, transplantation or other clinical applications of cells and tissues. The Guide refers to the requirements of the relevant EU directives but goes beyond them to describe generally accepted good practices at a technical level and includes consideration of some ethical issues.

In US, establishments that manufacture human cells, tissues or cellular or tissue-based products must comply with the ***Current Good Tissue Practice*** requirements under Title 21 Code of Federal Regulations, Part 1271

(https://www.ecfr.gov/cgi-bin/text-idx?SID=a8acdab7b2c8a28837844a9f5267debe&mc=true&node=pt21.8.1271&rgn=div5). Under the US Regulations, “manufacture” includes any or all steps in the recovery, processing, storage, labelling, packaging or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor. To facilitate compliance of the trade, the US Food and Drug Administration also issued guidance for the industry with nonbinding recommendations.

Annex D

List of Accreditation Organisations or Bodies for Reference

Foundation of the Accreditation of Cellular Therapy (FACT) is a non-profit corporation co-founded by the International Society for Cellular Therapy and the American Society of Blood and Marrow Transplantation for the purposes of voluntary inspection and accreditation in the field of cellular therapy. It establishes standards for high quality medical and laboratory practice in cellular therapies and provides accreditation services for cellular therapy and cord blood banks based on the FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration. The Joint Accreditation Committee-ISCT&EMBT (**JACIE**) also provides accreditation services for cellular therapy based on the same standards.

AABB* is an international, not-for-profit association representing individuals and institutions involved in the field of transfusion medicine and cellular therapies. It is committed to improving health by developing and delivery of standards, accreditation and educational programs that focus on optimizing patient and donor care and safety.

*AABB was the acronym for American Association of Blood Banks. However, to reflect more accurately its interests and diverse membership, the association changed its name in 2005 and is now known only as AABB.

American Association of Tissue Banks (AATB) is a professional, non-profit, scientific and educational organization. It is one of the national tissue banking organizations in the US. It is dedicated to improving health and saving lives by promoting the safety, quality and availability of donated human tissues. AATB publishes standards, accredits tissue banks and certifies personnel. The association also interacts with regulatory agencies and conducts educational meetings.