DEPARTMENT OF HEALTH

Report of the Working Group on Regulation of Premises Processing Health Products for Advanced Therapies

for submission to the Steering Committee on Review of Regulation of Private Healthcare Facilities

2014

CONTENTS

1 BACKGROUND

1.1. The Administration announced in October 2012 the establishment of the Steering Committee on Review of Regulation of Private Healthcare Facilities (Steering Committee) to conduct a review on 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 people's health.

1.2 At its first meeting on 2 November 2012, the Steering Committee set up four working groups to carry out focused study on four priority areas of concern regarding the provision of private healthcare facilities and to work out options on the way forward. Following the adverse incident in October 2012 resulting from invasive medical procedures provided by a beauty service company, it became evident that one of the priority areas of concern was to address the health risk brought by premises improperly processing health products for advanced therapies[1] through regulatory control.

1.3 The Working Group on Regulation of Premises processing Health Products for Advanced Therapies (Working Group) was thus formed and tasked to identify the range of health products for advanced therapies, examine the local situation, take reference of the experience in other jurisdictions in the regulation of premises processing cells, tissues and health products for advanced therapies and to propose necessary measures and appropriate regulatory control in Hong Kong.

[1] Health products for advanced therapies include gene therapy products, cell therapy products and tissue-engineered products for human use.

2 THE WORKING GROUP

Membership

2.1 The Working Group, chaired by Dr. Homer TSO, SBS JP, comprised 25 members, including 5 Steering Committee members and 20 co-opted members from academia in the fields of biotechnology and clinical research, relevant medical specialties and laboratory professions, trade and industry sector and consumer group. Membership list of the Working Group is attached at Annex I. The Working Group held a total of three meetings during the period from April 2013 to September 2013.

Terms of Reference (TOR)

2.2 At the first meeting of the Working Group, Members endorsed the following TOR as set out below –

(i) to define and come up with the range of health products for advanced therapies that could be conducted in laboratory/ambulatory setting; and

(ii) to examine whether and how to impose regulatory control on premises where health products for advanced therapies are stored and/or processed[2], having regard to the latest development in medical practice and technology, as well as overseas regulations and international best practices applicable to local circumstances.

[2] The original TOR of the Working Group also included the review of regulation of premises where high risk sterile products, e.g. cytotoxic drugs (those sterile products that may introduce risks during processing), are processed. However, it was later learned that another Working Group (on defining high-risk medical procedures/ practices performing in ambulatory setting) has already discussed the issue; therefore this Working Group did not examine this area.

3 RANGE OF HEALTH PRODUCTS FOR ADVANCED THERAPIES

3.1 During the meetings, Members surveyed the range of health products for advanced therapies available, or claimed to be available, on the local market as well as their regulation in other jurisdictions, including the United States (US), European Union (EU), Australia, Singapore, South Korea, the Mainland and Taiwan. Members noted that the following three procedures related to cell and tissue products are known to be available or promoted in Hong Kong, namely (i) platelet rich plasma therapy, (ii) autologous fat transfer, and (iii) stem cell therapies and transplantation.

3.2 In general, the technologies on health products for advanced therapies are diversified and are evolving rapidly; and the procedures related to cell and tissue products, including their collection, storage and manipulation, involve different levels of risk and require different levels of regulatory control. As such, instead of defining a range of health products for advanced therapies that could be processed in laboratory/ambulatory setting, Members agreed that the proposed regulatory control on cells, tissues and health products for advanced therapies should adopt a risk-based approach (i.e., "low" or "high" risk category) as determined by the extent of manipulation and the intended use. In addition, Members agreed that premises processing cells, tissues and health products for advanced therapies should also be regulated via a risk-based approach.

4 OVERVIEW OF REGULATORY CONTROL IN US, EU, AUSTRALIA, SINGAPORE, SOUTH KOREA, THE MAINLAND AND TAIWAN

4.1 Members were introduced to the regulatory control on the handling, processing and storing of human cells and tissues as well as human cell and tissue products for advanced therapies for human application in US, EU, Australia, Singapore,

South Korea, the Mainland and Taiwan. A summary of their regulatory control is provided in Annex II.

4.2 Members noted that the regulatory framework in US, EU, Australia, South Korea and Singapore share similar principles and adopt a risk-based approach with the level of control that commensurate with the degree of risk of the cells and tissues. The degree of risk is normally determined by the (i) intended use; and (ii) extent of manipulation of the cells and tissues. Regulatory guidelines are available to provide the definition of manipulation to decide whether the cells or tissues will be subject to additional control, e.g. pre-marketing approval.

4.3 Members also noted that in US, EU, Australia, South Korea and Singapore, human cells and tissues subject to minimal manipulation [3] and intended for homologous use[4] are usually considered as low risk category. For low risk category, the regulations focus on preventing disease transmission from donors to recipients; and ensuring the safety and quality of the human cells and tissues procured, processed, stored and distributed for human application. Common control measures include establishment registration, Good Tissue Practice (GTP)[5] or similar requirements on

[3] Taking into account the methodological complexity of the advanced therapy products, and in order to reduce the possible interpretations, it has been defined that certain manipulations with the cells and tissues are not to be considered as substantial. These include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, freezing, cryopreservation, and vitrification.

[4] Homologous use means the repair, reconstruction, replacement or supplementation of a recipient's cells or tissues with a product that performs the same basic 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).

5 Good Tissue Practice (GTP) governs the methods used in, and the facilities and controls used for, the manufacture of cells, tissues, and cell- or tissue-based products, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution.

the handling and storage of human cells and tissues, donor screening and testing to prevent the transmission of communicable diseases, labelling, adverse event reporting and record keeping of the human cells and tissues. The establishments are subject to inspection by regulatory authorities.

4.4 On the other hand, human cells and tissues that are substantially manipulated or intended for non-homologous use are considered as high risk category and subject to more stringent control. Examples of substantial manipulation include cell expansion (culture), genetic modification of cells, or differentiation with growth factors. Examples of substantially manipulated cells and tissues include cultured chondrocytes and stem cell-based products when their functional, structural or biological characteristics have been altered or modified. In general, the aforesaid human cells and tissues are regulated as drugs or medical devices by these authorities. As such, in addition to the control applicable to low risk category, these products are required to demonstrate clinical safety and efficacy in humans before their marketing. Investigational use of high risk cells and tissues for human applications also requires regulatory authorisation. Furthermore, manufacturer's licences are required for premises where such products are manufactured; and the processing or manufacturing of human cell and tissue products for advanced therapies should comply with the principles and guidelines for Good Manufacturing Practice (GMP)[6] for drugs or the International Organization for Standardization (ISO) 13485:2003 (Quality management systems requirements) for medical devices. The manufacturers are also

6 Good Manufacturing Practice (GMP) governs the quality assurance which ensures that products are consistently produced and controlled in accordance with the quality standards appropriate to their intended use. GMP includes a range of issues, e.g. personnel, facilities and equipment, documentation, control of materials, manufacturing processes, quality control, storage and self-audit.

subject to inspection by regulatory authorities.

4.5 In the Mainland and Taiwan, the regulations for cells, tissues and health products for advanced therapies are still under development; and clinical applications of cell and tissue products are currently regulated under the framework of clinical trial authorization; and compliance with the GTP (or equivalent requirements) and GMP is mandatory.

5 PROPOSED REGULATORY CONTROL

5.1 Members discussed the proposed regulatory framework on premises processing health products for advanced therapies including the definitions of cells, tissues and health products for advanced therapies, scope of control, exemptions from regulation, and interim measures to enhance the protection of public health before the new legislation is introduced.

5.2 Members agreed that the regulation on cells, tissues and health products for advanced therapies should aim to protect public health, but at the same time, should not hinder usual medical practice and scientific research and development in these areas. Hence, Members considered that exemptions should be provided to premises (i) where cells and tissues are used for research and for purposes other than application to the human body; (ii) where cells and tissues are collected by registered healthcare professionals or their authorized and trained personnel for the purpose of diagnosis or testing of medical condition of a patient in the course of medical treatment; and (iii) where cells and tissues are used as an autologous graft within the same surgical procedure by registered healthcare professionals and without any banking process (as the quality and safety considerations associated with this process are completely

different, and the whole process is performed under the supervision of the same healthcare professional). The scope of regulation should include:

(i) licensing of premises;

(ii) accreditation of premises by competent bodies;

(iii) compliance with applicable guidelines (e.g. GTP, GMP and Good Clinical Practice (GCP)[7]);

(iv) adverse incidents monitoring;

(v) personnel training;

(vi) import and export control; and

(vii) product registration.

For laboratory analysis and practice, the regulatory control should address the issues on personnel, equipment, working materials and environmental control to ensure the competency of the operators and compliance with international standards. As the advancement of cell and tissue technology is fast and diversified, it is important for the regulatory control to catch up with these latest developments. In summary, Members agreed to introduce a new legislation for long term regulatory control on cells, tissues and health products for advanced therapies.

5.3 In addition to the above, some Members highlighted that the proposed regulatory control should also consider a range of other issues such as:

[7] Good Clinical Practice (GCP) is a set of ethical and scientific quality requirements which must be observed for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials are credible.

(i) compliance with ISO standards[8] (e.g. ISO 15189[9] and ISO 13022[10]) and specific standards used by competent bodies (see Annex III);

(ii) examples of competent bodies for accreditation of premises processing cells, tissues and health products for advanced therapies (some Members commented that both overseas and local bodies with the appropriate competency could be considered in the proposed regulatory control);

(iii) processing of cells, tissues and umbilical cord in clean room environment with aseptic techniques;

(iv) storage and transportation of cells, tissues and health products for advanced therapies; and

(v) involvement of Medical Laboratory Technologists (MLT).

The premises involved in producing health products for advanced therapies are required to comply with the guidelines for GMP to ensure that production environment is free of germ and dust, waste disposal and infection control systems are in place with proper quality control measures. Besides, sufficient qualified and trained staff should be deployed to ensure the quality of products and that they are fit for their intended uses. ,.

5.4 Some Members noted that the Schedule in Supplementary Medical Professions Ordinance (CAP 359) stipulates the definition of MLT and its registration requirements and suggested that the MLT Board may provide a platform for the training of personnel

[8] ISO standards were developed by International Standards Organizations Technical Committee and have been implemented in over 200 countries.

[9] ISO 15189:2012 specifies the requirements for quality and competency to medical laboratories.

[10] ISO 13022:2012 specifies the risk management and requirements for processing practices for medical products containing viable human cells.

on processing cells, tissues and health products for advanced therapies. However, other Members opined that MLT are trained for laboratory analysis but not the processing of cells, tissues and other products such as health products for advanced therapies. In addition, the processing of cells, tissues and health products for advanced therapies will involve the latest technologies. Continuous education and training will be essential for the personnel to catch up with the advancement of technology. The requirements of Good Laboratory Practice (GLP)[11], GTP and GMP should also be strictly followed. Therefore, there should be a separate dedicated body to oversee the training and registration matters of personnel.

5.5 Some Members suggested that the authority under the new legislation should include competent experts and multi-disciplinary professionals to oversee the trade and technology related to cells, tissues and health products for advanced therapies. The new legislation should stipulate the implementation details, consequential amendments of the existing relevant legislations, and sanction for non-compliance including penalties by way of fine and license revocation. The Government should announce and advocate the Working Group's recommendations to the trade, academia, scientists, healthcare workers and public. The Government should also conduct impact assessment to provide a fair and accurate assessment on the potential number of premises that will be affected and on the impact to the trade.

5.6 In addition to the ultimate long term regulatory control, interim measures should also be introduced to fill the gap before the implementation of new legislation

[11] Good Laboratory Practice (GLP) is a quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported

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for effective protection of public health. The interim measures should be formally announced together with specific implementation date or timeline to facilitate the stakeholders to follow suit and compliance with the new measures.

5.7 Some Members suggested that there should be transitional registration of premises processing cells, tissues and health products for advanced therapies for human application so that the Government could have information on their numbers in the market before the new legislation is introduced. During the transitional period, the Government will launch promotional campaign to educate the public and the trade on the potential risks associated with the processing of cells, tissues and health products for advanced therapies.

6 OVERALL VIEW

Long-term goals

6.1 Members generally agreed that cells, tissues and health products for advanced therapies for both medical treatments and clinical trials as well as all processes including the collection and donation of cells and tissues should be regulated in Hong Kong. Members acknowledged that the regulatory control on cells, tissues and health products for advanced therapies should adopt a risk-based approach (i.e. classified into low risk and high risk categories) as determined by the extent of manipulation and the intended use; and considered that the premises processing cells, tissues and health products for advanced therapies should be regulated accordingly.

6.2 Cells, tissues and health products for advanced therapies (usually for high risk

category) that fall within the definition of pharmaceutical products under the Pharmacy and Poisons Ordinance (Cap. 138) will be subject to the requirements of product registration, licensing of the manufacturing facilities, compliance with the Guidelines for GMP, and import and export control. Besides, the Government has planned to introduce a new legislation to regulate medical devices.

6.3 Members reached the consensus that there should be a new legislation with an overarching authority to effectively regulate cells, tissues and health products for advanced therapies in Hong Kong.

Interim measures

6.4 Before introduction of the new legislation, there should be interim measures in place backed up by the existing regulatory control for pharmaceutical products (drugs) to ensure the effective protection of public health:

(i) For low risk category, including

- advocating the premises to obtain accreditation from the relevant competent bodies (e.g. AABB, AATB and FACT in US; JACIE and WMDA in Europe; and NATA in Australia[12]);
- promulgating Guidelines for GTP or GMP or their equivalents for the industry to follow;
- promotional campaign to increase the awareness of the trade and the public on the potential risks associated with the processing of cells, tissues and health products for advanced therapies;

(ii) For high risk category, including

- licensing requirements of the manufacturing facilities for drugs;
- compliance with the Guidelines for GMP for drugs;
- regulation of clinical trials for drugs;
- continue the regulation of health products for advanced therapies as drugs if they fall under the definition of pharmaceutical products. Such

[12] AATB refers to the American Association of Tissue Banks, FACT is the Foundation for the Accreditation of Cellular Therapy (USA), JACIE is The Joint Accreditation Committee – ISCT & EBMT (ISCT is the International Society of Cellular Therapy and EBMT is the European Group for Blood and Marrow Transplantation), WMDA is the World Marrow Donor Association, and NATA is the National Association of Testing Authorities (Australia). Details of these competent bodies are provided at Annex III.

controls include the registration of products, licensing of facilities, and import/export controls;

- voluntary listing for medical devices, if the health products for advanced therapies fall within the definition of medical device under the Medical Device Administrative Control System and meet the listing requirements.

7 RECOMMENDATIONS

7.1 The following recommendations are put forward for the consideration of the Steering Committee -

(i) The ultimate goal of the regulatory control is (a) to establish a sound regulatory framework to control the whole spectrum of activities related to cells, tissues and health products for advanced therapies (including the use of human cells and tissues for cosmetic purposes) and (b) to ensure the safety, quality and efficacy of cells, tissues and health products for advanced therapies for human application without hindering their research and development.

(ii) In line with international practice, the scope of control should include the premises involved with the donation[13], procurement[14], testing, processing[15], preservation[16], storage[17], and distribution[18] of cells, tissues and health products for advanced therapies for human application.

(iii) The definitions for "cells", "tissues" and "health products for advanced therapies" in the scope of control are proposed as follows:

(A) "cells" mean 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 and cord blood, but not including (a) gametes[19] , (b) embryos outside

[13] Donation means donating human tissues or cells intended for human applications.

[14] Procurement means a process by which tissue or cells are made available.

[15] Processing means all operations involved in the preparation, manipulation, preservation and packaging of tissues or cells intended for human applications.

[16] Preservation means the use of chemical agents, alterations in environmental conditions or other means during processing to prevent or retard biological or physical deterioration of cells or tissues.

[17] Storage means maintaining the product under appropriate controlled conditions until distribution.

[18] Distribution means transportation and delivery of tissues or cells intended for human applications

[19] Gametes and embryos refer to those intended to be used for the purposes of any reproductive technology procedure, embryo research, surrogacy arrangement or other relevant activities regulated under the Human Reproductive Technology Ordinance (Cap. 561).

the human body[20], or (c) blood and blood components[21];

(B) "tissues" mean all constituent parts of the human body formed by the cells, but do not include (a) gametes, (b) embryos outside the human body, or (c) organs[22] or parts of organs if their functions to be used have the same purposes as the entire organs in the human body; and

(C) "health products for advanced therapies" include gene therapy products, cell therapy products and tissue-engineered products for human use. Animal cells or tissues used in health products for advanced therapies for human application are also included..

Recommendation (1): Cells, tissues and health products for advanced therapies for both medical treatments and clinical trials should be regulated with a regulatory framework to ensure public health and safety. All processes on cells, tissues and health products for advanced therapies for human application including donation, procurement, testing, processing, preservation, storage, and distribution should be subject to regulation.

20 See footnote 19.

21 Blood means whole human blood collected from a donor and processed either for transfusion or for further manufacturing into pharmaceutical products. Blood component means a therapeutic constituent of human blood that can be prepared by various methods, but not including lymphocytes intended for use for the purpose of haematopoietic stem cell transplantation.

22 Differentiated part of the human body, formed by different tissues, that maintains its structure, vascularization, and capacity to develop physiological functions with a significant level of autonomy.

(iv) The regulatory control should adopt a risk-based approach as determined by the extent of manipulation and intended uses:

(A) "low risk category" refers to cells, tissues and health products for advanced therapies that are subject to minimal manipulation and intended for homologous use; and

(B) "high risk category" refers to cells, tissues and health products for advanced therapies that are subject to more than minimal manipulation (i.e. substantial manipulation) or intended for non-homologous use.

Recommendation (2): Cells, tissues and health products for advanced therapies should be regulated according to their risks as determined by the extent of manipulation and the intended use of such products.

(v) A new legislation with an overarching regulatory framework of identified control scope and measures should be introduced to achieve the ultimate goal. The framework should include:

(A) Mandatory licensing requirements for the premises processing cells, tissues and health products for advanced therapies;

(B) Accreditation of premises by competent bodies;

(C) Compliance with the relevant guidelines, e.g. GTP or GMP or GCP or equivalent guidelines;

(D) Adverse event reporting system;

(E) Adequate and appropriate training for personnel processing cells, tissues and health products for advanced therapies;

(F) Import/export controls; and

(G) Registration requirements for cells, tissues and health products for advanced therapies.

Recommendation (3): The Working Group recommends the Administration to introduce a new legislation with an overarching authority to effectively regulate cells, tissues and health products for advanced therapies through a comprehensive set of regulatory controls including licensing requirements for premises, accreditation of premises, compliance with guidelines, adverse event reporting, designation of Person-in-Charge, staffing requirement and training, import and export control, and registration of health products for advanced therapies.

(vi) The following premises should be exempted from the proposed regulatory framework:

(A) where cells and tissues are used for research and for purposes other than application to the human body (e.g. in-vitro research or in animal models, in-vitro diagnostic devices);

(B) where cells and tissues are collected by a registered medical practitioner, a registered dentist, a registered or enrolled nurse, or a trained person authorized by a registered medical practitioner or a registered dentist for the purpose of diagnosis or testing of medical condition of a patient in the course of medical treatment; and

(C) where cells and tissues are used as an autologous graft (tissues removed and transplanted back to the same individual) within the same surgical procedure by a registered medical practitioner or a registered dentist and without any banking process.

Recommendation (4): Premises processing cells and tissues for research purposes other than application to human body, for diagnosis of a patient in the course of medical treatment by registered professionals or where cells and tissues are used as an autologous graft within the same surgical procedure by registered professionals without any banking process should be exempted from the regulatory controls for advanced therapies.

(vii) It is noted that before the new legislation is introduced, the Department of Health can implement the following interim measures to enhance the protection of public health:

(A) Advocating the premises processing cells, tissues and health products for advanced therapies to obtain accreditation from relevant competent bodies;

(B) Promulgating guidelines for GTP or GMP or their equivalents for the industry to follow;

(C) Conducting promotional campaign to increase the awareness of the trade and the public on the potential risks associated with the processing of cells, tissues and health products for advanced therapies

(D) Continuing the regulation of health products for advanced therapies that fall under the definition of pharmaceutical products, including the registration of products, licensing of facilities, and import/export controls.

(E) Encouraging the listing of health products for advanced therapies that are classified as medical devices under the Medical Devices Administrative Control System.

Recommendation (5): The Working Group recommends the Administration to implement interim measures on the processing of cells, tissues and health products for advanced therapies to enhance public health before the new legislation takes effect.

Chairman,
Working Group on Regulation of Premises
Processing Health Products for Advanced Therapies

ANNEX I - Composition of the Working Group

Chairperson:

Dr. Homer TSO, SBS JP

Members:

Steering Committee members
Ms Jasminia Kristine CHEUNG
Mr Andy LAU
Director of Health/ Representative - Ms Linda WOO, Assistant Director (Drug)
Chief Executive, Hospital Authority/ Representative - Dr H W LIU, Director (Quality & Safety)
Head of Healthcare Planning and Development Office, Food and Health Bureau/ Representative - Mr Chris SUN Yuk-han, JP

Co-opted members
Mr CHAN Wing-kwong
Mr CHANG Hsiu-kang
Dr Celine CHENG
Ms Bella HO Shiu-wun
Dr LAM Tak-sum, JP
Mr Arthur LAU
Professor Kenneth LEE Ka-ho
Professor LEE Shui-shan
Dr LEE Cheuk-kwong
Professor Ronald Adolphus LI
Mr Alex LI Wai-chun
Dr Sian NG Chor-shan
Dr Cecilia PANG Wai-bing
Dr Jonathan SHAM Shun-tong, JP
Dr Dominic TSANG Ngai-chong
Professor TSE Hung-fat
Professor Ian WONG Chi-kei
Dr Raymond WONG Siu-ming
Dr WONG Yiu-chung
Professor Albert YU Cheung-hoi

ANNEX II – Summary on the regulation of human cells, tissues and health products for advanced therapies outside Hong Kong

(A) Regulatory regimes of US, EU, Australia, South Korea and Singapore on cells, tissues and health products for advanced therapies

General principles (risk-based approach)

Low risk category	***High risk category***
Scope: • Cells and tissues subject to **minimal manipulation** and intended for **homologous use**	Scope: • Cells and tissues that are **substantially manipulated** or intended for **non-homologous use**
Focus of regulation: • Prevent disease transmission from donors to recipients • Ensure the safety and quality of human tissues and cells procured, processed, stored and distributed for use in humans	Focus of regulation (in addition to those for low risk category): • also require to demonstrate clinical safety and efficacy of human cells and tissues for use in humans before their marketing • Investigational use of high-risk human tissues and cells in human will also require regulatory authorisation

Regulatory framework

Low risk category	***High risk category***
US • Solely under the legislation for human cells, tissues, and cellular and tissue-based products	*US* • Also under the legislation for biological products, drugs and/or devices
EU • Solely under the legislation for human cells and tissues	*EU* • Also under the legislation for medicinal products
Australia • Under a single biological framework for regulating all human cells and tissues – Classes 1 and 2	*Australia* • Under a single biological framework for regulating all human cells and tissues – Classes 3 and 4
South Korea • Under the legislation for human tissues	*South Korea* • Under the legislation for pharmaceutical products
Singapore • a draft framework for tissue-based therapeutic products regulated under the legislation for health products – Categories 4 and 3	*Singapore* • Currently regulated under the legislation for medicinal products • a draft framework for tissue-based therapeutic products regulated under the legislation for health products –

	Categories 2 and 1 • Clinical use of high-risk tissue-based therapeutic products requires special service license

Key regulatory requirements in US

Low risk category *[Relevant legislation:* *Public Health Service Act;* *Title 21 (Food and Drugs) of the Code of Federal Regulations (CFR), Part 1271 Human Cells, Tissues, and Cellular and Tissue-based Products]*	***High risk category*** *[Federal Food, Drug, and Cosmetic Act;* *Title 21 of the CFR, Part 207, 210, 807, 820, etc]*
Premises • Establishment registration and product listing with FDA • Site inspection by FDA on need basis	Premises • Establishment registration and product listing with FDA • Site inspection by FDA
Premarket review/authorization • No	Premarket review/authorization • Through Biologics Licence Application for biological drugs, or Premarket Approval (PMA) or Premarket Notification 510(k) for devices
Donor screening and testing • Yes	Donor screening and testing • Yes
Good practice/standards • Compliance with the cGTP	Good practice/standards: • Compliance with the cGTP • Compliance with cGMP for drugs and Quality System Regulation for medical devices • Investigational use either through the exemption under the Investigation New Drug (IND) for drugs or Investigational Devices Exemption (IDE) for devices
Others • Adverse events (AE) reporting • Maintaining a tracking system • Retaining of records at least 10 years	Others • AE reporting • Maintaining a tracking system • Retaining of records at least 10 years • Labelling requirements

Key regulatory requirements in EU

Low risk category *[EU Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells (with 2006/17/EC and 2006/86/EC)]*	***High risk category*** *[EU Directive 2001/83/EC on the Community code relating to medicinal products for human use (with Regulation (EC) No 1394/2007)]*
Premises • Accreditation, designation, authorisation or licensing of tissue establishments • Site inspection at least biennially	Premises • Accreditation, designation, authorisation or licensing of tissue establishments/ manufacturers applicable to medicinal products • Site inspection at least biennially
Premarket review/authorization • Verification of compliance with requirements in the Tissues and Cells Directive	Premarket review/authorization: • Verification of compliance with requirements in the Tissues and Cells Directive • Marketing authorisation requirements applicable to medicinal products
Donor screening and testing • Yes	Donor screening and testing • Yes
Good practice/standards • Compliance with the safety and quality standards set out in the Tissues and Cells Directive	Good practice/standards: • Compliance with the Tissues and Cells Directive • Compliance with GMP requirements applicable to medicinal products
Others • AE reporting, Traceability, Keeping data for full traceability for a min. of 30 years after clinical use	Others • AE reporting, Traceability, Keeping data for full traceability for a min. of 30 years after clinical use • Other requirements applicable to medicinal products (e.g. clinical trial authorisation, pharmacovigilance…)

Key regulatory requirements in Australia

Low risk category (Class 1 and 2[23]) *[Therapeutic Goods Act 1989 (with The Australian Code of GMP for Blood and Blood Products)]*	***High risk category (Class 3 and 4)***

[23] In Australia, biologicals (items made from, or containing, human cells or human tissues for use in a person) are classified into four Classes. Class 1 is of the lowest risk while Class 4 the highest.

Premises • Licensing of manufacturer by TGA (except for Class 1 biologicals) • Site inspection by TGA	Premises • Same requirements as that for Class 2 biologicals • Site inspection by TGA
Premarket review/authorization • Evaluation of dossier (for Class 2 biologicals) or technical master file (for HPC) submission by TGA	Premarket review/authorization • Dossier submission with nonclinical and clinical data for evaluation of product quality, safety and efficacy by TGA
Donor screening and testing • Yes	Donor screening and testing • Yes
Good practice/standards • Australian Code of GMP for human blood and tissue • Product-specific standards	Good practice/standards: • Australian Code of GMP for human blood and tissue • Product-specific standards
Others • AE reporting	Others • AE reporting

Key regulatory requirements in South Korea

Low risk category *[Safety, Management, etc. of Human Tissue Act]*	***High risk category*** *[Pharmaceutical Affairs Act]*
Premises • Tissue bank required to obtain authorization from the Minister of Health and Welfare • Site inspection by Minister of Health and Welfare	Premises • Establishment registration and product listing with Korea FDA • Site inspection by KFDA
Premarket review/authorization • No	Premarket review/authorization • Applicable to pharmaceutical products
Donor screening and testing • Yes	Donor screening and testing • Yes
Good practice/standards • Compliance with the requirements set by the Minister of Health and Welfare	Good practice/standards: • Compliance with the requirements set by the Minister of Health and Welfare • Compliance with GMP and GCP
Others • AE reporting • Record keeping	Others • AE reporting • Record keeping • Labelling requirements

Key regulatory requirements in Singapore

Low risk category (Category 3 and 4[24]) *[Health Products Act]*	***High risk category (Category 1 and 2)***
Premises • Licensing of manufacturer by HSA • Site inspection by HSA	Premises • Licensing of manufacturer by HSA • Site inspection by HSA
Premarket review/authorization • Product registration (except Category 4 products)	Premarket review/authorization • Product registration
Donor screening and testing • Yes	Donor screening and testing • Yes
Good practice/standards • Singapore's MOH guidelines for tissue banking as GTP for donation, screening, testing, processing, storage, labelling and distribution of human tissues and cells	Good practice/standards: • Singapore's MOH guidelines for tissue banking as GTP for donation, screening, testing, processing, storage, labelling and distribution of human tissues and cells • GMP compliance
Others • ADR reporting • Patient registry for some products (e.g. heart valve)	Others • ADR reporting • Patient registry • Service licensing • Clinical trial certification

Summary of overseas regulatory requirements

Low risk category	***High risk category***
Premarketing review: • Not required in US and South Korea • Verification required in EU & Australia	Premarketing review: • Generally regulated as drug or medical device, will require product registration
Premises: • Subject to establishment licensing control & site inspection	Premises: • Subject to establishment licensing control & site inspection • Compliance of GMP for drugs; or ISO 13485:2003 or equivalent for medical devices
Donor screening and testing	Donor screening and testing
GTP or similar requirements on handling and storage	GTP or similar requirements on handling and storage
Labeling	Labeling
Adverse event reporting	Adverse event reporting

[24] In Singapore, cell- and tissue-based therapeutic product (CTT) are classified into four Categories. Category 1 is of the highest risk while Category 4 the lowest.

Good records & traceability	Good records & traceability
Personnel training [in EU]	Personnel training [in EU]

(B) Administrative and statutory regulation of cells, tissues and health products for advanced therapies in Mainland and Taiwan

In Mainland and Taiwan, the regulation for cells, tissues and health products for advanced therapies are under development and are currently regulated as conducting clinical trials of cells and tissues.

Situation in Mainland

- 分別發布《血站管理辦法》、《采供血機構設置規劃指導原則》、《臍帶血造血干細胞庫管理辦法(試行)》、《臍帶血造血干細胞治療技術管理規範》、《醫療技術臨床應用管理辦法》、《干細胞臨床試驗研究管理辦法(試行)》、《非血緣造血干細胞移植技術管理規範》、《非血緣造血干細胞采集技術管理規範》等規範性文件以加強干細胞及體組織的采集、運輸、制備、檢測、儲存、發放、機構授權、應用等的監管。
- 衛生和計劃生育委員會負責對涉及重大倫理問題、高風險、安全有效性尚需進一步驗證和需要使用稀缺資源的第三類醫療技術(於《醫療技術臨床應用管理辦法》中定義)制定目錄和進行臨床應用管理。
- 第三類醫療技術包括
  - 克隆治療技術、
  - 自體免疫細胞 （T 細胞、NK 細胞）治療技術、
  - 細胞移植治療技術（幹細胞除外）、
  - 臍帶血造血幹細胞治療技術、
  - 造血幹細胞（臍帶血除外）治療技術、
  - 組織工程化組織移植治療技術等。
- 第三類醫療技術首次應用於臨床前，必須經過衛生部組織的安全性論證和倫理審查。
- 醫療機構向技術審核機構提出審核申請時
  - 要有在該機構註冊的、能夠勝任該項醫療技術操作的專業技術人員；
  - 有相應的設備和設施；該醫療技術要通過該機構醫學倫理審查；
  - 在臨床試驗研究時有安全有效的結果；
  - 還要有與該項技術相關的管理制度和品質保障措施等。
  - 申請技術審核時，醫療機構應提交該技術的國內外應用情況、適應症、禁忌症、不良反應、技術路線、品質控制措施、療效判定標準、評估方法，與其他醫療技術診療同種疾病的風險、療效、費用及療程比較等。
- 若有關產品屬藥品或醫療器械，則受法規《中華人民共和國藥品管理法》或《醫療器械監督管理條例》所監管。

Situation in Taiwan

- 根據《人體試驗管理辦法》第 2 條， 醫療機構將新醫療技術列入常規醫療處置項目前，應施行人體試驗研究。
- 體細胞(somatic cell)治療屬於新醫療技術，故在體細胞治療技術應用於病患治療前，需經人體試驗驗證其安全與療效。
- 台灣衛生署對體細胞治療技術之管理，是依據醫療法第 78 條規定，由教學醫院擬定計畫並提經機構審查會同意後，報請衛生署核准執行，計畫核准前之審查則照新藥實施之程序審查方式進行。

- 台灣衛生署於 2002 年公告了人體細胞組織優良操作規範（Good Tissue Practice），作為機構操作處理人體細胞組織的品質安全依據。
- 若產品屬藥品或醫療器材，則受《藥事法》監管。

ANNEX III - Examples of competent overseas bodies providing accreditation to companies and their major accreditation services

Name / Country or region / Accreditation cycle	Description of organization	Accreditation activities	Basis for accreditation [Assessment tools]
American Association of Blood Band (AABB) USA 2 years	Founded in 1947, a non-profit organization aims to provide standard for voluntary compliance, accreditation services, education and training.	Accreditation program include: - Donor centers: collection, processing, testing, distribution - Transfusion services: testing (pre-transfusion, compatibility), blood administration - Cellular therapy (HPCs, Cord Blood, Somatic Cells) - Immunohematology reference laboratory, Relationship/parentage testing, perioperative Services & SBB schools	Compliance with AABB Standards, Code of Federal Regulations, CLIA'88 federal guidance document [Audit of the quality and operational systems]
American Association of Tissue Banks (AATB) USA 3 years	Founded in 1976, a non-profit organization aims to provide standard for voluntary compliance accreditation services, education and training.	Accreditation program include: - Tissue bank - Tissue distribution intermediary, or dispensing service	Compliance with AATB standard [Pre-inspection checklist & on-site inspection]
Foundation for the Accreditation of Cellular Therapy (FACT) USA 3 years	Co-founded by ISCT & ASBMT in 1996, a non-profit organization aims to provide standard setting, accreditation services, education and training	Accreditation program include: - Cord blood banks - Cellular therapy accreditation for clinical program, collection facilities: marrow or apheresis, and processing facilities	Compliance with FACT standards[25] [Written information from applicant facility and on-site inspection]

[25] Including (1) FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration ; and (2) NetCord-FACT International Standards for Cord Blood Collection, Processing and Release Administration.

Name / Country or region / Accreditation cycle	Description of organization	Accreditation activities	Basis for accreditation [Assessment tools]
International NetCord Foundation Europe 3 years	Founded in 1997, a non-profit association aims to provide standards and accreditation for umbilical cord blood banks.	Accreditation activities include: - Umbilical cord blood banks	Compliance with NetCord-FACT standards[26] [Written information from applicant facility and on-site inspection]
The Joint Accreditation Committee-ISCT (Europe) & EMBT (JACIE) Europe 4 years	Co-founded by ISCT (Europe) and EMBT in 1998, a non-profit body aims to provide assessment and accreditation in the field of HSC transplantation	Four areas of activities in allogeneic or autologous transplantation for adult or pediatric patients: - Clinical - HPC, marrow collection - HPC, apheresis collection - Processing	Compliance with FACT-JACIE standards[27]
World Marrow Donor Association (WMDA) Europe "Qualification" stage 2 to 5 years "Accreditation" stage Every 4 years	A global association aims to provide standard setting, accreditation services, education and training for HSC donor registries	Accreditation activities include: - HSC donor registries	First cycle (Qualification) Compliance with a subset of WMDA Standards "benchmark standards" [Annual self-evaluation] Subsequent cycles (Accreditation) Compliance with full WMDA Standards [Annual self-evaluation and on-site inspection]

[26] NetCord-FACT International Standards for Cord Blood Collection, Banking, and Release for Administration

[27] FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration

Name / Country or region / Accreditation cycle	Description of organization	Accreditation activities	Basis for accreditation [Assessment tools]
Eye Bank Association of America (EBAA) USA 3 years	A nationally-recognized accrediting body for eye banks aims to provide standard setting, advocacy & education, and accreditation services	Accreditation program include: - Facilities that provide human eye tissue for surgical use, research and ophthalmic training - Eye bank (recovery, processing, tissue storage, final distribution, tissue evaluation, and donor eligibility determination).	Compliance with EBAA Medical Standards and Procedures for Procurement, Preservation, Storage and Distribution of Human Eye Tissue for Transplantation and Research. [On-site inspection]
National Association of Testing Authorities, Australia (NATA) Australia 3 years (for medical testing accreditation)	An authority responsible for the accreditation of laboratories, inspection bodies, calibration services, producers of certified reference materials and proficiency testing scheme providers	Laboratory accreditation in more than 15 different fields and programs, including Medical Testing (Accreditation of an Human Progenitor Cell processing facility is represented at 10.30.25 Progenitor cell transplantation procedures of Medical Testing field)	Compliance with International standard ISO 15189 (Medical Testing), OECD Principles of Good Laboratory Practice (GLP Recognition), and other applicable practice For accreditation in medical testing, compliance with ISO 15189 and applicable National Pathology Accreditation Advisory Council (NPAAC) standards and other applicable practice. NPAAC standard, Requirements for procedures related to the collection, processing, storage and issue of human haemopoietic progenitor cells, is applicable to facilities processing haemopoietic progenitor cells (HPCs) and lymphocytes used for cellular therapy.

Abbreviations: ASBMT = American Society of Blood and Marrow Transplantation; EMBT = European Group for Blood and Marrow Transplantation; HPC = Hematopoietic Progenitor Cells; HSC = Hematopoietic Stem Cell; ISCT = International Society for Cellular Therapy.

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