

Regulation of Cell- and Tissue-based Therapeutic Products

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Outline

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 - **Product categories**
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 - **Regulation of clinical trials**
 - **Regulation of clinical use**



A Statutory Board of the Ministry of Health

The Singapore Public Service

Health Sciences Authority



Vision



To be the **LEADING**
INNOVATIVE AUTHORITY
protecting and advancing **NATIONAL HEALTH** and **SAFETY**

Mission

- To **wisely regulate** health products
- To **serve** the administration of justice
- To **secure** the nation's blood supply
- To **safeguard** public health



Corporate Headquarters • Health Products Regulation Group • Blood Services Group • Applied Sciences Group

Our Functions & Roles



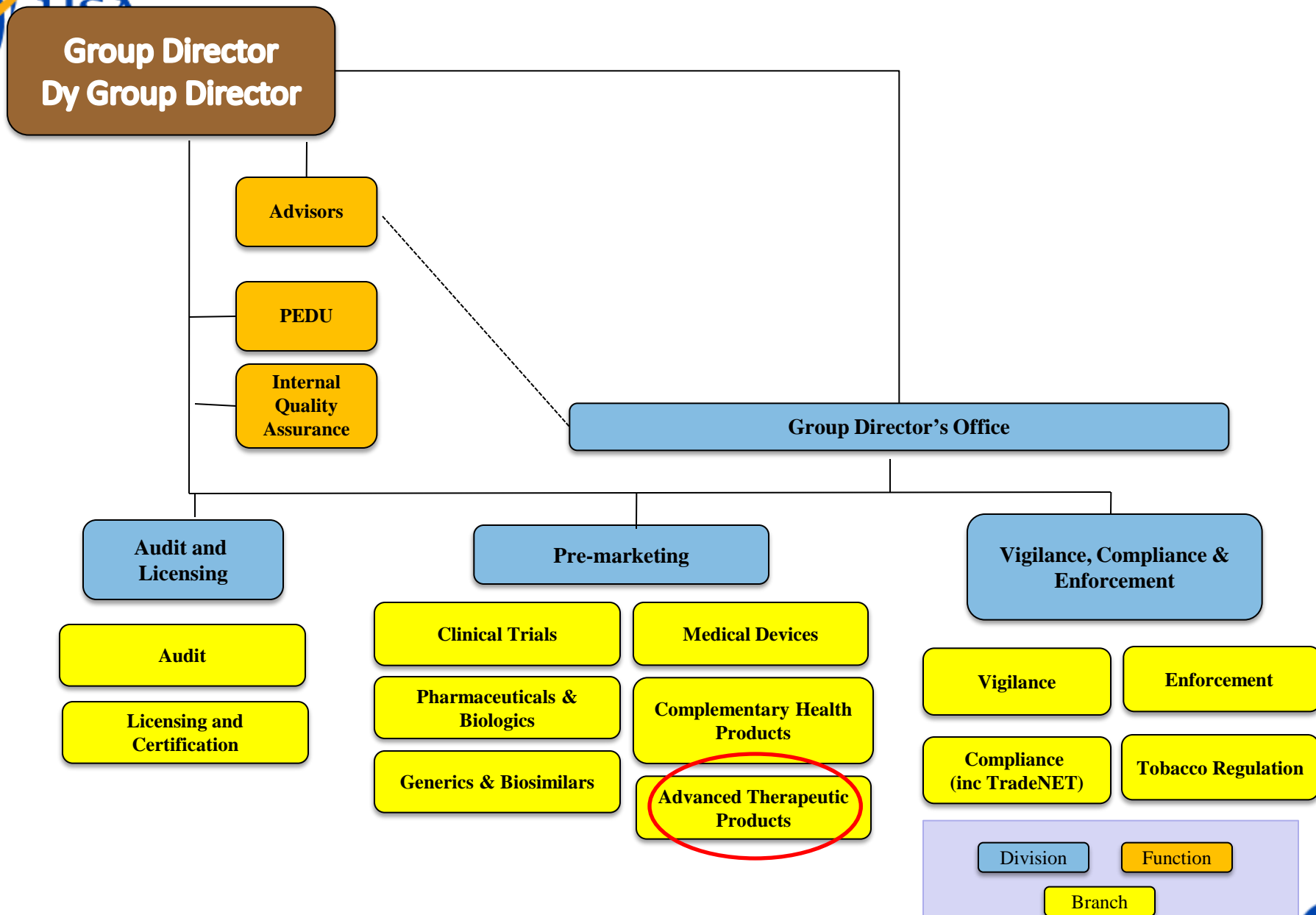
Options for new & greater synergies across Groups



Health Products Regulation Group



Ensures that drugs, innovative therapeutics, medical devices and health-related products in Singapore are wisely regulated to meet appropriate standards of safety, quality and efficacy throughout the product life cycle



Proposed regulation of human cell and tissue-based therapeutic products in Singapore

Introduction

- **Human cell and tissue-based therapeutic (CTT) products, are regulated as biologics medicinal products by HSA under the Medicines Act**
 - A risk-based tiered approach is being applied to the regulation of CTT products
- **Ministry of Health (MOH) will regulate the clinical use of CTT product**
 - All registered practitioners must get CTT specialised service / special care service license from MOH before administering such products into their patients under the Private Hospitals and Medical Clinics Act (PHMCA)

Introduction

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Legislation

- **Medicines Act (MA)**
 - Act enacted in 1975
 - Manufacture, import, wholesale supply and product license and clinical trials of medicinal products
 - Western pharmaceuticals including biologics and CTT products, among other medicinal products
 - *High-risk CTT products are currently regulated while low-risk CTT products in the later-phase (regulations under the Health Products Act)*
 - *Guidance on Medicinal Products Registration (April 2011)*
 - *Pre-market and post-market license requirements*

Legislation

- **Health Products Act (HPA)**
 - Enacted on 1 November 2007
 - Intent of the Act

“An Act to regulate the manufacture, import, supply, presentation and advertisement of health products and of active ingredients used in the manufacture of health products....”

*The Acts can be viewed at the Attorney General’s Chambers URL
(<http://statutes.agc.gov.sg/aol/home.w3p>)*

Introduction

- **Health Products Act (HPA)**
 - Main Act provides for key controls
 - licensing of activities – manufacture, import, wholesale supply
 - registration of health product
 - prohibition on false or misleading advertisement
 - Specific requirements are prescribed in the subsidiary legislations (SL)
 - Medical Device
 - Cosmetic Products
 - **Therapeutic Product**
 - **Cell and Tissue-based Therapeutic Product**

Definition (draft)

Cell- and tissue-based therapeutic product means a health product that contains or consists of autologous, allogeneic human cell, tissue or their derivative or xenogeneic that is –

- used for or administered to humans; or
- intended to be used for or administered to humans,

for one or more of the following purposes or has one or more of the following effects when used in or on humans –

- preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, defect, ailment, injury, or the symptoms thereof;
- replacing, modifying, influencing, inhibiting, restoring, correcting, altering or supporting the anatomy or of a physiological process;
- supporting or sustaining life;
- testing the susceptibility of humans to any disease or disorder; or
- any revision or change in human condition, including any revision or change in the appearance, colour, texture, structure or position of any bodily feature of a person

including any autologous, allogeneic or xenogeneic cell, tissue or their derivative that is intended to be used in the manufacture of a cell- and tissue-based therapeutic product

Xenogeneic product (draft)

“xenogeneic” is a reference to an article that contains or consists of a live cell, tissue, organ or their derivative from a non-human animal source that is intended to be used as an active ingredient intended to be used for or administered to humans

Exclusion – human organ

excludes –

- **any human organ intended for transplantation to replace a corresponding diseased organ;**

“organ” refers to perfusable human organ intended for direct donor-to-recipient transplantation, whether whole or in parts, and whose specific function is intended to return after revascularization and reperfusion. It includes any adjunct blood vessels that are retrieved together with the organ for use in transplantation. Examples include kidney, heart, liver, lungs, pancreas, and any portion of the gastrointestinal tract

Exclusion – blood and blood components

excludes –

- any cell- and tissue-based therapeutic product that is a whole blood or blood components intended for treating blood disorders and that
 - has not been subject to substantial manipulation; and
 - is intended solely for homologous use; or
 - is not intended for aesthetic procedures

Substantial manipulation

- ‘Substantial manipulation’ means processes (except *in-vitro* culturing of human oocyte fertilized with human sperm intended for assisted reproduction technology procedures) that include, but not limited to –
 - cell expansion;
 - encapsulation;
 - genetic modification; or
 - any processing that alters the biological, physiological or structural characteristics of cells or tissues, or characteristics of the tissue relating to the tissue’s utility for reconstruction, repair or replacement

CTT product categories

- **HP (CTT) Regulations is proposed to include four CTT product categories with the level of regulation based on:**
 - **degree of manipulation;**
 - **intended use (whether homologous or non-homologous);**

CTT product categories

- **Category 1 CTT product means a cell-and tissue-based therapeutic product that achieves its primary intended action in or on the human body by physiological, pharmacological, immunological, or metabolic means; AND**
 - has been subject to substantial manipulation; or
 - is intended for a non-homologous use
- **Category 2 CTT product means a cell-and tissue-based therapeutic product that does not achieve its primary intended action in or on the human body by physiological, pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means; AND**
 - has been subject to substantial manipulation; or
 - is intended for a non-homologous use

CTT product categories

- **Category 3** CTT product means a cell-and tissue-based therapeutic product that
 - has NOT been subject to substantial manipulation; and
 - is intended solely for a homologous use
- **Category 4** CTT product means a cell-and tissue-based therapeutic product that is not a
 - Category 1, Category 2, or Category 3 cell-and tissue-based therapeutic product

Regulations on manufacture

- **Manufacturer's licence (ML) required**
- **ML linked to product registration except when**
 - **manufactured at the request of a qualified practitioner and administered to the patient in a licensed healthcare establishment under the supervision of that qualified practitioner**
 - **supplied solely for export purpose**

Manufacturing standards

- **Manufacturers**
 - PIC/S GMP Standards
 - Other standards as deemed appropriate for the product category
 - GTP (currently HSA will adopt MOH guidelines for tissue banking) for donation, screening, testing, processing, storage, labeling and distribution of cells and tissues
 - ISO 13485
- **Importers and Wholesalers**
 - Comply with HSA Guidance on GDP & other standard obligations specified in the Regulations
- **Records to be maintained indefinitely**

Registration of CTT products

- **Product registration required for marketing in Singapore**
 - **Exceptions:**
 - **Unregistered CTTs manufactured under contractual agreement with healthcare institutions**
 - **Named-patient use subject to approval by the Authority**
 - **Export of unregistered CTTs subject to approval by the Authority**
 - **Category 4 CTT product**

Dossier requirements - registration

Documents	Location in		Module/Part required
	ICH CTD	ACTD	
Administrative Documents	Module 1	Part 1	Yes
CTD Overview and Summaries	Module 2	<i>Incorporated in Parts 2, 3 and 4</i>	Yes
Quality documents	Module 3	Part 2	Full quality module
Non-clinical documents	Module 4	Part 3	Full non-clinical module
Clinical documents	Module 5	Part 4	Full clinical module

Pharmacovigilance requirements

- **Due to the novelty and complexity, CTT products are viewed as potentially higher risk products with different safety concerns. These include**
 - early complications such as infectious disease transmission
 - late complications such as malignant diseases and emerging latent diseases
- **Current systems of detecting safety issues are still applicable to CTT products**

Enhanced vigilance requirements

- **Pre-market licensing conditions**
 - Risk management plan
 - Submission of global PSURs
 - Provision of product sales data
 - Provision of educational materials to physicians
 - Specific post-marketing follow-up of patients for products that may have potential for long term complications
 - PILs for patients
- **Post-market licensing conditions**
 - Serious Adverse Event reporting
 - Patient registry

Adverse effects

- **Applies to all licensees & registrants**
- **Duty to maintain records of defects and adverse effects**
 - maintain records of supply indefinitely
- **Reporting of defects and adverse effects**
 - Reporting timeframe
 - For serious ARs which involves transmission of an infectious disease or disease agent or is the result of a systematic failure: within 48 hours after the licensee or registrant first becomes aware of event
 - For serious ARs: within 7 days after the licensee/registrant first becomes aware of the event
 - For others: within 14 days after the licensee/registrant first becomes aware of the event

** Serious ARs: an AR which results in a person's death, threaten a person's life, results in hospitalization or prolongs hospital stay, results in persistent or significant disability or incapacity, results in congenital anomaly or birth defect*

Patient registry

- **Mandated under the regulations**
 - All high-risk CTT products (cell based vaccines, stem cell products, tissue engineered products etc)
 - Some low-risk CTT products such as implants of human origin (e.g. processed human allograft, human heart valve)
- **To serve as a patient exposure database for:**
 - Determining incidence of adverse reactions
 - Vigilance & surveillance
 - Future epidemiological study collaborations with existing registries e.g. National Registry of Diseases, National Death Registry, National Birth Defect Registry and the Communicable disease Centre to track long-term outcomes of patients

Information captured in registry

Patient

- Patient identifier
- Age
- Ethnic group
- Gender
- Indications for the HCT product
- Medical history (including concomitant medications and relevant information)

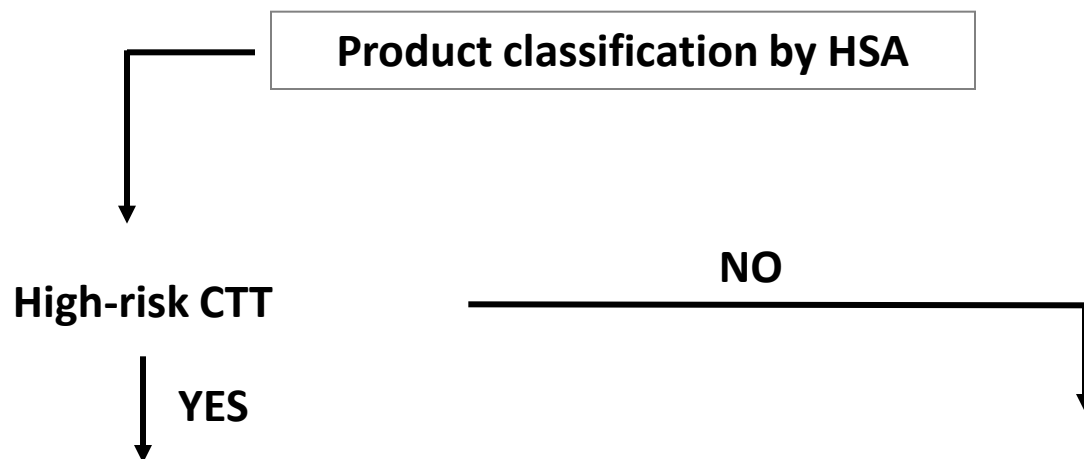
Product

- Product Description
- Brand name (if applicable)
- Batch identifier/number
- Dosing Regimen (Dose, route of administration, Frequency)
- Start date and end date
- Duration of therapy
- Name of cell processing lab

Doctor

- Doctor identifier
- Place of Practice
- Name of company (for clinical trials)
- Name of applicant (for clinical trials)
- Contact of applicant (for clinical trials)

Regulation of clinical trials



Regulation by IRB and HSA

Clinical trial certificate (CTC) is required

GMP compliance

- ❖ applicable for processes involving substantial manipulation

Serious AR reporting

Patient registry

Regulation by IRB

CTC is NOT required

Dossier requirements – clinical trials

- **Protocol**
- **Investigator's brochure**
- **Information on product manufacturing process**
 - Details of cell/tissue procurement
 - Donor screening and testing (mandatory for allogeneic source)
 - Cell source and cell bank
 - List of reagents and certificate of analysis
 - Cell/tissue manipulation process; *ex vivo* expansion, activation etc
 - Product release specifications; identification, purity, potency, sterility, impurities/residual antibiotics
 - Test methods
 - Final product formulation
 - Storage, packaging, shelf-life, shipping and handling

Introduction

- Human cell and tissue-based therapeutic (CTT) products, including hematopoietic stem cells, are regulated as biological medicinal products by HSA under the Medicines Act
 - A risk-based tiered approach is being applied to the regulation of CTT products
- **MOH will regulate the clinical use of CTT product**
 - All registered practitioners must get CTT specialised service / special care service license from MOH before administering such products into their patients under the Private Hospitals and Medical Clinics Act (PHMCA)

Regulation of Clinical Use of CTT

Application for MOH CTT specialized service license



Product classification by HSA

MOH will review the scientific evidences

MOH CTT Service Licensing T&C applicable to all service licenses

For high risk CTT products (additional controls)

- GMP compliance
 - applicable for processes involving substantial manipulation
- Serious ADR reporting and patient registry

Questions?