Singapore's New Cell, Tissue and Gene Therapy Products Regulations

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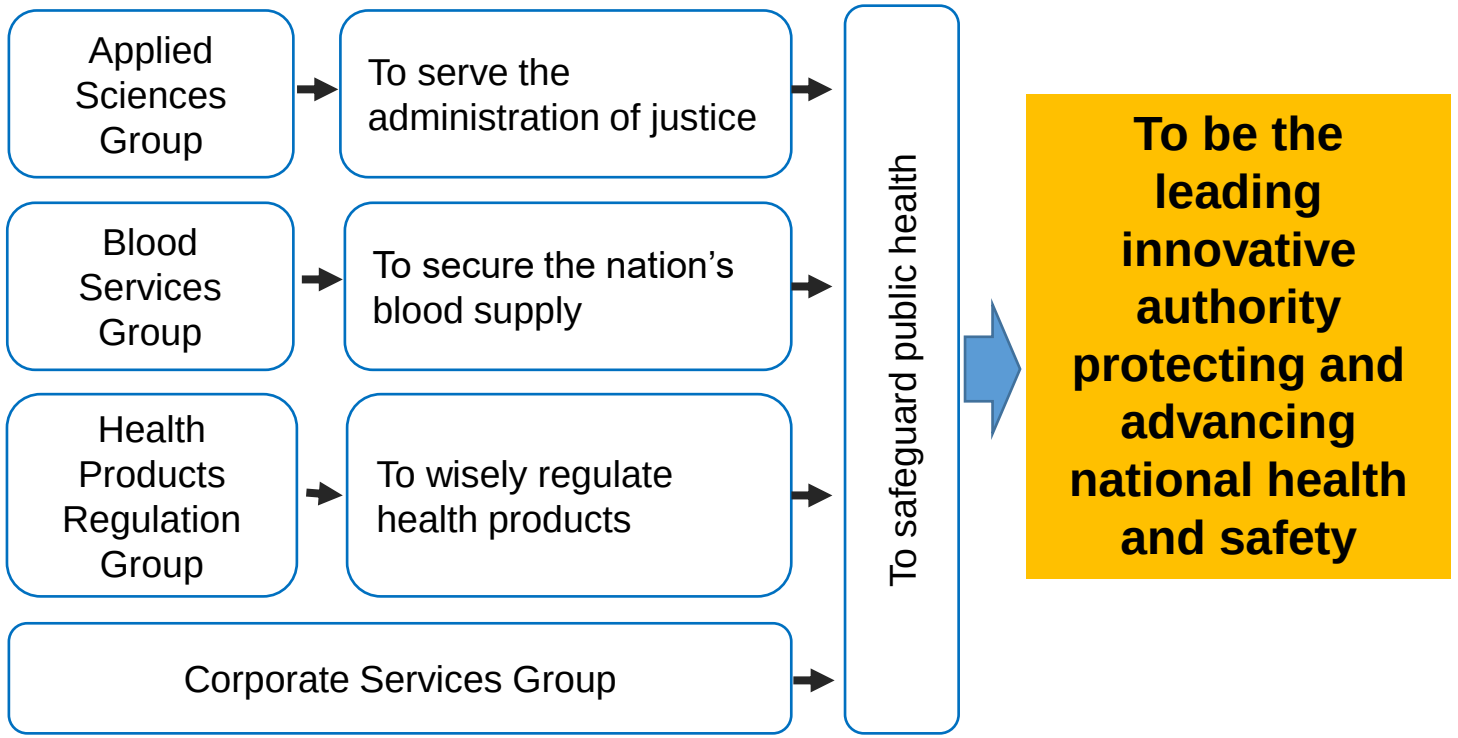
Outline

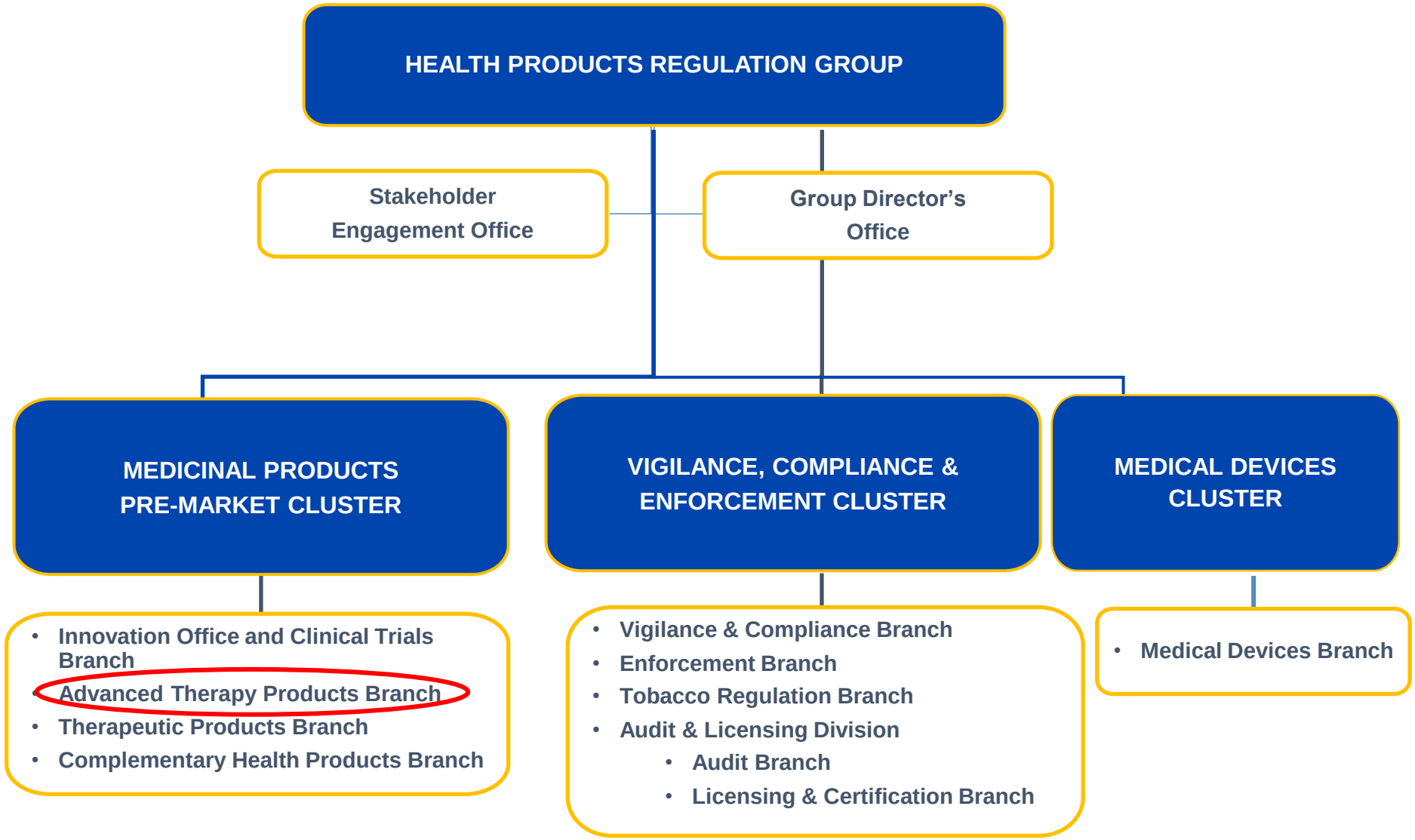
- Health Products Act
- CTGT product definition and exclusion
- CTGT product classification
- Regulatory control of Class 1 and Class 2 CTGTP
- Traceability requirements for CTGTP
- Tight control on healthcare institutions manufacturing of CTGTP
- Exemption order – 2 years grace period for existing manufacturers
- Tight regime for unregistered Class 2 CTGTP special access route
- Exemption order – import and supply of out-of-specifications CTGTP
- Regulation of clinical trials

HSA: A unique blend of scientific expertise

The **Health Sciences Authority (HSA)** was established on 1 April 2001 as a statutory board under MOH



Health Products Regulation Group



Health Products Act and Regulations

- Health Products Act (HPA) - 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 and provide for matters connected therewith.
  - enacted in 2007
  - apply to the categories of health products that are specified in the First Schedule of the Act
    1. Medical device
    2. Cosmetic product
    3. Therapeutic product
    4. Oral dental gum
    5. **Cell, tissue or gene therapy product**

Regulations

72.—(1) The Authority may, with the approval of the Minister, make regulations for carrying out the purposes and provisions of this Act.

Health Products Act – 'health-related purpose'

"health-related purpose" means a therapeutic, preventive, palliative, diagnostic or cosmetic purpose, or any other purpose for the promotion or preservation of human health and well-being, and includes the following:

(*a*) preventing, diagnosing, monitoring, treating, curing or alleviating any disease, disorder, ailment, injury, handicap or abnormal physical or mental state, or the symptoms thereof, in humans;

(*b*) compensating for any injury or handicap in humans;

(*c*) investigating, modifying or replacing any part of the human anatomy or any physiological process in humans;

(*d*) testing the susceptibility of humans to any disease, disorder or ailment;

(*e*) influencing, controlling or preventing conception in humans;

(*f*) testing for pregnancy in humans;

(*g*) inducing anaesthesia in humans;

(*h*) destroying or inhibiting micro-organisms that may be harmful to humans; and

(*i*) cleansing, fragrancing, deodorising, beautifying, preserving, improving, altering or restoring the complexion, skin, hair, nails or teeth of humans;

Cell, Tissue and Gene Therapy Products Regulations under the Health Products Act

Legislation to Effect CTGTP Implementation

No.	Legislation
1	Health Products Act
2	Health Products (Cell, Tissue and Gene Therapy Products) Regulations
3	Health Products (Advertisement of Specified Health Products) Regulations
4	Health Products (Licensing of Retail Pharmacies) Regulations
5	Health Products (Clinical Trials) Regulations
6	Health Products (Clinical Research Materials) Regulations
7	Health Products (Exemptions) Order
8	Health Products (Existing Manufacturers of CTGTP - Exemption) Order (till Feb 2023)
9	Health Products (Composition of Offences) Regulations
10	Health Products (Medical Devices) Regulations
11	Interpretation (Health Sciences Authority Act – Fees) Order

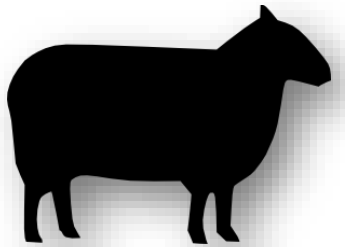
Objectives of CTGTP Regulations

- Provide a pro-innovation environment with a regulatory framework that is ‘fit-for-purpose’ and least burdensome, yet safeguarding public health and safety with appropriate controls, as these therapies are novel, innovative and typically very expensive
- Facilitate successful product development from clinical trials, manufacturing (both commercial and healthcare institutions) and registration of CTGTP, including long term follow-up for safety and efficacy

What is a CTGTP?

Cell, tissue or gene therapy product is a health product that contains:

OR



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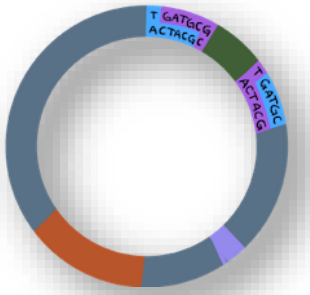


human cells or tissue (viable or non-viable)

animal cells or tissue (viable),

recombinant nucleic acids *i.e. genetically modified DNA or RNA as carriers of a therapeutic gene (transgene)*

is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose

CTGTP – HPA Schedule 1 Definition

"5. Cell, tissue or gene therapy product	(1) "Cell, tissue or gene therapy product" means any substance that —

(a) is intended for use by and in humans for a therapeutic, preventive, palliative or diagnostic purpose, including any of the following purposes:

(i) for preventing, diagnosing, treating, curing or alleviating any disease, disorder, injury, ailment, handicap or abnormal physical or mental state, or any symptom thereof;

(ii) for replacing, repairing, regenerating or reconstructing any anatomy, or for modifying or replacing any physiological process;

(iii) for regulating, repairing, replacing, adding or deleting a genetic sequence or modifying genetic material;

(iv) for supporting or sustaining life;

(b) has as a constituent any of the following substances or combination of substances:

(i) viable or non-viable human cells or tissues;

(ii) viable animal cells or tissues;

(iii) recombinant nucleic acids, where the effect of the recombinant nucleic acid relates directly to the recombinant nucleic acid sequence that it contains or to the product of the genetic expression of its sequence;

(c) achieves its primary intended action by pharmacological, immunological, physiological, metabolic or physical means, leading to its use for a therapeutic, preventive, palliative or diagnostic purpose; and

(d) is not any of the following:

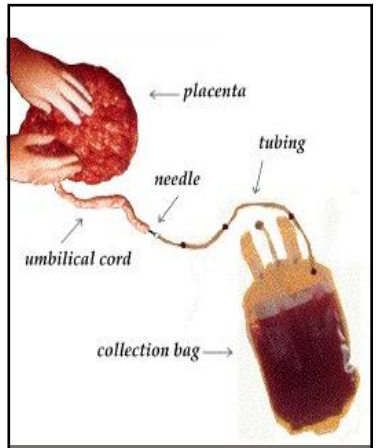
CTGTP – exclusions

The following are excluded as they are covered under other legislation – Private Hospitals and Medical Clinics Act or HPA

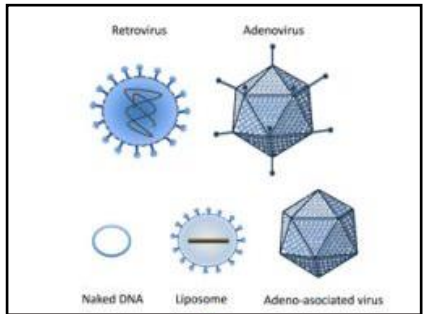
Excluded CTGTP
A recombinant vaccine for a preventive purpose
An *in-vitro* diagnostic product
Bone marrow, peripheral blood or umbilical/placental cord blood from a human that is minimally manipulated and intended for homologous use
Cells and tissues obtained from a patient that are minimally manipulated and re-implanted for homologous use into the same patient during the same surgical procedure
Organs and tissues that are minimally manipulated and intended for transplant
Reproductive cells (sperm, eggs) and embryos for assisted reproduction
Whole blood and any blood component that is minimally manipulated and intended for treating blood loss or blood disorders

CTGTP Regulated under the Framework

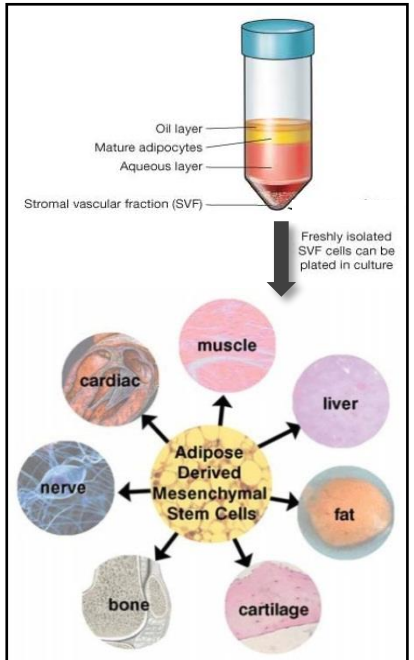
- Demineralised bone matrix and bone grafts
- Stem cells
  - bone marrow or cord blood
  - adipose (fat) tissue
- Amniotic membrane with/without cells
- Cultured skin and cartilage
- Cells on scaffold/matrix
- Viable animal cells
- Viral/non-viral vectors with a therapeutic gene
- Gene modified cells (including chimeric antigen receptor cells and gene edited cells)
- Embryonic- or induced pluripotent-derived products



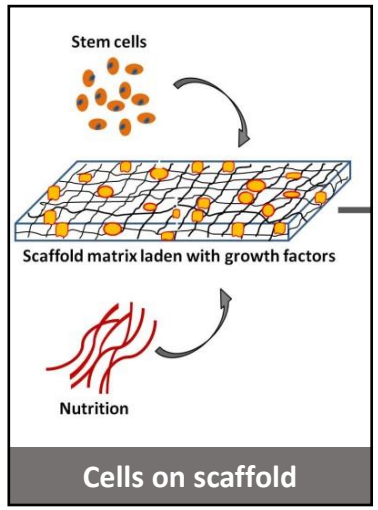
Cord blood stem cells



Gene delivery systems for therapeutic applications

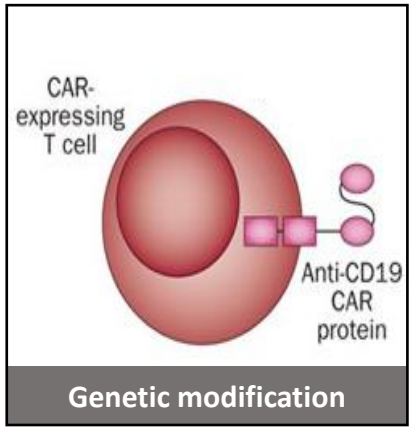


Mesenchymal stem cells



Cells on scaffold


Human bone allograft



Genetic modification

Sources: http://www-bioon.qiniudn.com/industry/UploadFiles/201410/2014101317353859.jpg
http://www.plasticsurgerypulsenews.com/2/article_print.php?QnArticleID=34
http://www.usacordbloodbank.com/the-cord-blood-stem-cell-collection-process/
http://investor.zimmerbiomet.com/releasedetail.cfm?ReleaseID=836517

HP (CTGTP) Regs

Parts	Regulations
Part 1	Preliminary
Part 2	CTGTP Manufacture – Licensing and Exceptions
Part 3	CTGTP Import – Licensing and Exceptions
Part 4	CTGTP Supply – Licensing and Exceptions
Part 5	CTGTP Supply Requirements
Part 6	Presentation of CTGTP
Part 7	Registration of CTGTP
Part 8	Duties and Obligations of Manufacturers, Importers, etc., of CTGTP
Part 9	Certification
Part 10	General Provisions
The Schedule	Fees

CTGT Product Classification

Criteria for Product Classification

DEGREE OF PROCESSING

- Minimal vs. not minimal manipulation

INTENDED USE

- Performs same function and administered at the same anatomical or histological environment in recipient

COMBINATION

- Combined with a therapeutic product or a medical device

SOURCE

- Human, Animal or Recombinant nucleic acids

Criteria for Product Classification

Degree of Processing

Minimal manipulation

In relation to a cell or tissue (but not a gene), means processing the cell or tissue by way of any process so that the biological characteristics or functions of the cell or the structural properties of the tissue (as the case may be) are not altered, such as by:

cutting/sizing, grinding, shaping, centrifugation, disinfection by soaking in antibiotic or antimicrobial solution, sterilization or irradiation, cell separation, concentration or purification, filtration, lyophilization, freezing, cryopreservation or vitrification

Not minimal manipulation

Examples: cell expansion, cell activation, encapsulation, cells grown on scaffold, genetic modification

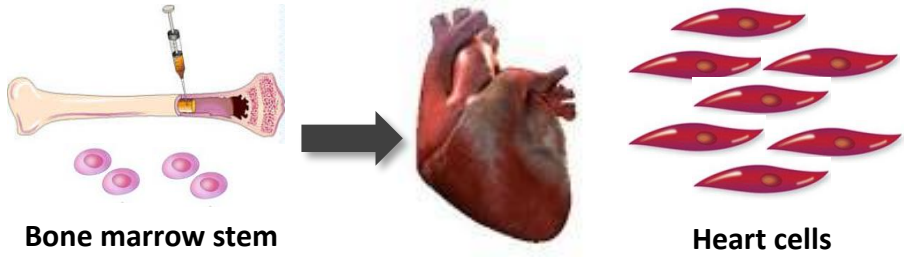
Criteria for Product Classification

Intended Use

Bone chips and cubes for orthopaedic indications

Homologous use

means the CTGT product **performs the same basic function** or functions **in the recipient as** the original cells or tissue **in the donor in the same anatomical or histological environment.**



Bone marrow stem cells

Heart cells

Non-homologous use

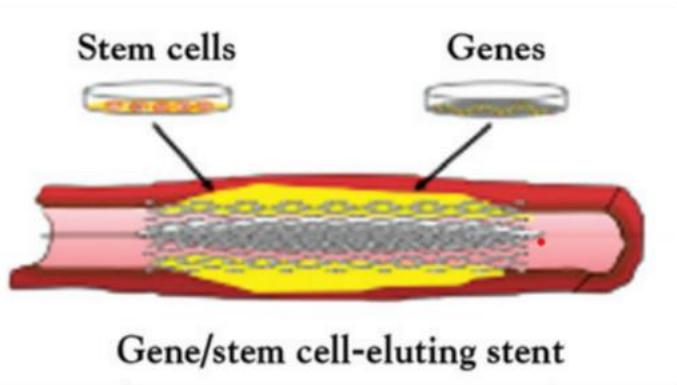
CTGT product performs a **different function or** administered at **a different anatomical/histological environment** in the recipient.

Criteria for Product Classification

Combination

Not combined

Cells and tissues **not combined** with a therapeutic product (TP) or medical device (MD)



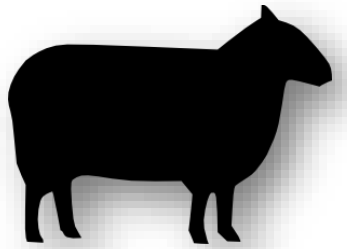
Combined

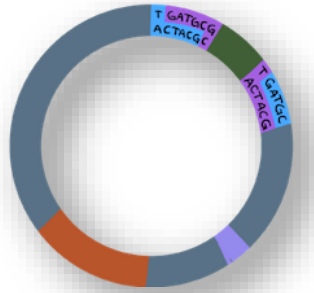
Cells and tissues **combined** with a therapeutic product or medical device

K Yin, DK Agrawal. Curr res Cardiol 2014;1:93

Criteria for Product Classification

Source





viable animal cells or tissue (xenogeneic)	recombinant nucleic acids
Animal cells presents these risks: • risk of viruses and other harmful agents being transmitted from animal cells – introduce infection across species barriers • immunological rejection	The gene is usually delivered using a carrier, called a vector. The most common vectors are viruses, which presents the following risks: • unwanted immune reaction • infection caused by the virus • possibility of causing a tumor • integration into host genome and passing to off-springs

CTGTP – Risk-based Classification

Class 1 CTGTP (lower risk)	Class 2 CTGTP (moderate to high risk)
"Class 1 CTGT product" means a CTGT product that — • is the result of only minimal manipulation of human cell or tissue; • is intended for a *homologous use*; • is *NOT combined* with a TP or a MD; and • is assigned by the Authority as a Class 1 CTGT product due to a lower health risk to a user of the product e.g. bone grafts, amniotic membrane, skin	"Class 2 CTGT product" means a CTGT product other than a Class 1 CTGT product e.g. cell therapy, tissue engineering, gene therapy and xeno-based products

CTGTP Regulatory Controls

Regulatory Controls of Class 1 and Class 2 CTGTP

All CTGTP are prescription only medicine. The extent of controls are calibrated to the product risk class.

Activities	Class 1 CTGTP	Class 2 CTGTP	
		Minimally manipulated for non-homologous use*	All other Class 2 CTGTP
Dealer licences	Excepted, notify – known dealers	Excepted, notify – known dealers	All relevant licences required – licenced dealers
Product registration	Excepted, notify	Required to register	Required to register
Clinical trials	NA (regulated under HBRA)	CTA/CTN required	CTA/CTN required
CRM notification	Applicable if dealer's notification not submitted under CTGTP Regs	Applicable	Applicable
Duties and obligations	Applicable	Applicable	Applicable

***e.g. minimally manipulated cord blood for treating cerebral palsy**

Clinical trials authorisation (CTA)/notification (CTN)

Traceability requirements for Class 1 and Class 2 CTGTP

Division 1 — General duties

31. Routine inspections, etc.
32. Duty to maintain records of manufacture
33. Duty to maintain records of receipt and supply
34. Duty to maintain system of traceability
35. Duty to maintain records of defects and adverse effects
36. Duty to report defects and adverse effects
37. Duty to notify Authority concerning recall

Duty to maintain system of traceability *

34.—(1) Every manufacturer, importer, supplier or registrant of a CTGT product must establish and maintain a system of traceability that complies with paragraph (2).

(2) The system mentioned in paragraph (1) must at the minimum enable the traceability of the CTGT product and its starting and raw materials, including all substances that may come into contact with the cells or tissue it contains during any of the following processes:

(*a*) sourcing;

(*b*) procurement;

(*c*) processing;

(*d*) testing;

(*e*) packaging;

(*f*) storage;

(*g*) transport;

(*h*) delivery to the licensed healthcare institution or the licensed retail pharmacy where the CTGT product is used, administered, supplied or disposed, as the case may be.

where the records relate to traceability, to be kept for at least 30 years after the expiry date of the CTGT product or any other shorter period that the Authority allows in a particular case

*also applicable to CT and CRM

Tight Control on HCIs Manufacturing Class 2 CTGTP

- Many CTGTP use patients' own cells as starting materials
- Each patient-specific batch is *de novo* synthesised from the starting material to final product – cell procurement, expansion, genetic modification (live viruses or viral vectors) to formulation, storage and release. This ready availability of 'ingredients' and 'patient specificity' makes healthcare institutions (HCI) manufacturing of CTGTP possible
- Hence, the following two measures are imposed:
  - Manufacture under GMP conditions and obtain ML – more than minimal manipulation
  - Collect data on quality, safety, clinical outcomes and cost effectiveness and other requirements[#]

[#] Directive under PHMCA on the use of CTGTP manufactured in-house by HCI was implemented on 1 Feb 2021

Exemption Order – 2 Years Grace Period for Existing Manufacturers

Existing manufacturers manufacturing a 'relevant CTGT product' are exempted for 2 years from requirements under HPA sections 12(1) (manufacture), 13(1) (import for manufacture) and 14(1) (wholesale supply). They can continue to manufacture the products in those premises, while ramping up to meet CTGTP GMP standards

They should be making a relevant CTGTP that:

- is more than minimal manipulation of any cell or tissue; and
- is intended for clinical supply

Citation and period in force

1.—(1) This Order is the Health Products (Existing Manufacturers of CTGT Products — Exemption) Order 2021.

(2) This Order is in force for 2 years starting 1 March 2021.

Tight Regime for Unregistered Class 2 CTGTP Special Access Route

To minimise indiscriminate import and use of unregistered CTGTP and that they are extremely expensive, HSA has instituted a tight regime for special access route (SAR, named-patient import).

To allow only on a case-by-case basis for specific patients, as treatment of last resort, subject to the following conditions being met:

- The product is approved by TGA, EMA, HC, MHRA or US FDA and is from the same approved manufacturing site
- The product should be used in accordance with the instructions provided in the package insert
- Basic quality is assured through review of Certificate of Analysis, which is to be submitted upon import
- Doctor informs patient that the product is not registered and that the QSE is not evaluated by HSA
- Collect data on patient safety, clinical outcomes and report serious adverse events
- The use is approved by the clinical ethics committee and relevant professional board

Duty to obtain consent and provide information for supply of unregistered Class 2 CTGT products in certain circumstances

17.—(1) A person may only supply an unregistered Class 2 CTGT product under regulation 21 or 22 to a patient if the person obtains consent from the patient for the supply of that CTGT product to that patient in accordance with paragraph (2).

(2) A patient's consent mentioned in paragraph (1) may be obtained only after the patient has been informed of all of the following:

(*a*) that the CTGT product to be supplied to the patient is not registered with or approved by the Authority;

(*b*) that the safety, efficacy and quality of the CTGT product to be supplied to the patient has not been evaluated by the Authority.

Summary of Key Controls – CTGTP Regulations

Activities	Class 1 CTGTP	Class 2 CTGTP
Research/Clinical trials	Human biomedical research, HBRA (MOH)	Clinical trials authorisation/notification under HP (CT) Regs
Manufacture's licence (ML)*	Excepted, notify HSA (Good tissue practice or other stds) – minimal manipulation	Required (CTGTP GMP) – not minimal manipulation
Import's licence (IL)	Excepted, notify HSA (Good distribution practice, GDP) – minimal manipulation	Required (GDP) – not minimal manipulation
Wholesale supply (WSL)	Excepted, notify HSA (GDP) – minimal manipulation	Required (GDP) – not minimal manipulation
Product registration	Excepted, notify HSA and acceptance of notice required prior to supply	Required
Advertising	No advertisement to public	No advertisement to public
Serious AE reporting	Required	Required
Product traceability	Records kept for at least 30 years after product expiry or shorter period as specified by HSA	Records kept for at least 30 years after product expiry or shorter period as specified by HSA
Special access route-SAR (unregistered Class 2 CTGTP)	Not applicable	SAR IL required, and to inform and obtain consent from patient – product is not registered, and safety, efficacy & quality is not evaluated by HSA

*** 2 year exemption for existing manufacturers of manufacturing not minimally manipulated CTGTP**

Note: Class 2 that is minimally manipulated for non-homologous use – dealer licences excepted, product registration apply (cord blood for cerebral palsy)

GMP and GDP Guidelines

HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

01 MARCH 2021

GUIDELINES ON GOOD MANUFACTURING PRACTICE FOR CELL, TISSUE AND GENE THERAPY PRODUCTS

"Good Manufacturing Practice Standard" means any of the following as shown on the Authority's website:

(*a*) the Good Manufacturing Practice Standard for CTGT products issued by the Authority;

(*b*) any other good manufacturing practice standard that is approved by the Authority;

HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

MARCH 2021

GUIDANCE NOTES ON GOOD DISTRIBUTION PRACTICE

12 HANDLING OF CELL, TISSUE AND GENE THERAPY PRODUCTS (CTGTP), AND ACTIVE SUBSTANCES / STARTING MATERIALS OF CTGTP

12.1 There must be an effective, risk-based quality system which adequately assesses the risks that impacts product quality; considers the proper controls and mitigation measures; as well as putting in place the appropriate communications and active process reviews, to ensure maintenance of appropriate storage and distribution conditions for the CTGTP with its active substances and starting materials (hereinafter known as "products"). The level of effort, formality and documentation should commensurate with the

CMC Guidelines for Clinical Trials and Registration

APPENDIX 8 CHEMISTRY, MANUFACTURING AND CONTROLS REQUIREMENTS FOR CELL, TISSUE OR GENE THERAPY PRODUCTS FOR CLINICAL TRIALS AND PRODUCT REGISTRATION

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Import and Supply of Out-of-Specifications CTGTP

- The product release specification is approved by HSA for both investigational and registered products
- Due to the unique nature of CTGTP, there are occasions when the manufactured product is not in full compliance with the release specifications **(e.g. viability, cell dose)** – out-of-specifications (OOS)
- Therefore, administration of an OOS CTGTP should be in the best interest of the patient and that administration is the correct course of action, as assessed by the treating physician
- Under HPA, import and supply of an unwholesome product is prohibited. Hence, an exemption order has been drafted to exempt the dealers from the prohibition provided the conditions for import and supply are met

Exemption Order – Import and Supply of Out-of-Specifications CTGTP

Out-of-specifications CTGT products

4.—(1) In this paragraph —

"out-of-specifications CTGT product" or "OOS CTGT product" means a CTGT product that —

(*a*) is not a result of only minimal manipulation of cell or tissue;

(*b*) is autologous and contains viable human cells or tissue; and

(*c*) is unwholesome because of section 2(2)(*d*)(i) or (ii) of the Act;

Guidance for Industry – Reporting and Recall of Defective TP & CTGTP Mar 2021

Annex II – Conditions for supply of out of specification batch of CTGTP

The following guidelines would apply for the local supply of out of specification CTGTP for clinical trials and clinical use:

(*d*) a health product is unwholesome if —

(i) it is not in conformity as regards strength, quality or purity with the specifications of its manufacturer;

(ii) it has a strength which differs from, or a standard of purity or quality which falls below, that which is represented on its label;

(iii) any of its constituent substances or ingredients, as stated on its label, has been extracted or omitted from it;

(iv) it contains any prohibited substance or any substance in excess of the prescribed permitted concentration;

(v) it consists in whole or in part of any filthy, putrid or decomposed substance;

(vi) it has been manufactured or stored under unsanitary conditions;

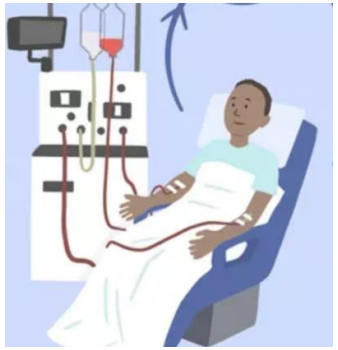
(vii) it has been kept in a package which is composed in whole or in part of any substance which may render the contents injurious to health;

(viii) it has been packed with any substance so as to reduce the purity, quality, strength or beneficial properties that it would have had if it had not been so packed; or

(ix) it has passed its expected useful life or its expiry date as assigned by its manufacturer.

Import and Supply of Out-of-Specification CTGTP – flow

Trial subject/patient



T-cells

Manufacturer for CTGTP manufacturing

OOS identified after product manufacture

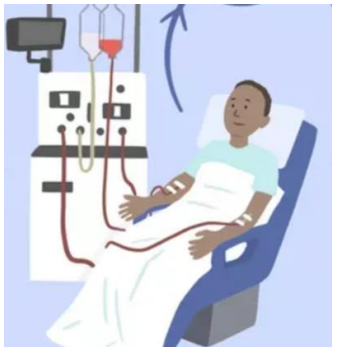
Conducts and provides the risk assessment

Requests release

Informs HCP

Product released

Directly from manufacturer, or thru an importer, wholesaler or trial sponsor



Trial subject/patient

Administers the product after:

1. Evaluated the benefit/risk
2. Notified IRB (for clinical trials)
3. Obtained consensus from clinical ethics committee and endorsement from an independent specialist (for clinical practice)
4. Informed the subject or legal rep in the case of clinical trials and obtained written consent
5. Informed the patient in the case of clinical practice and obtained written consent

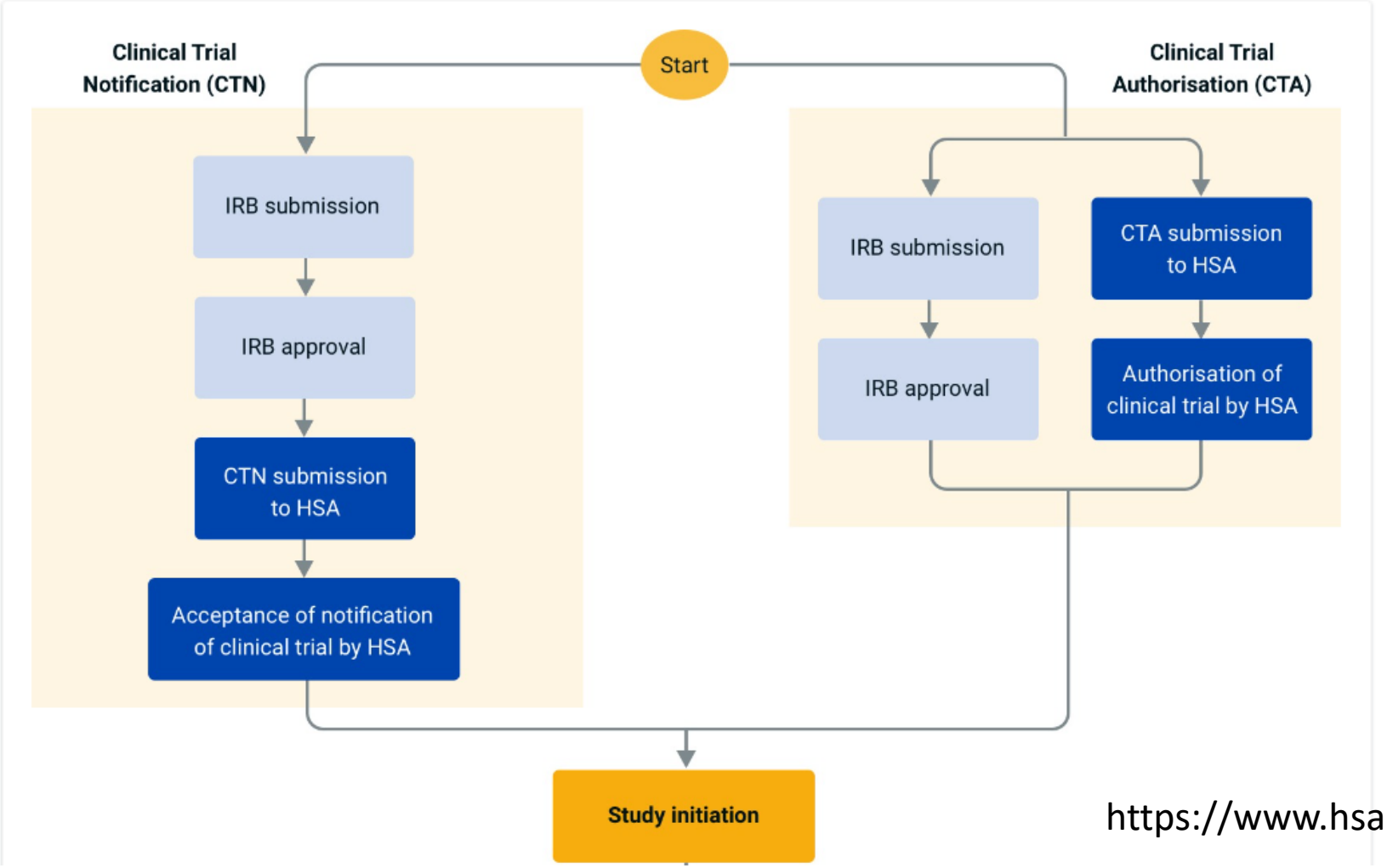
Informs HSA 48 hrs after administering the product (guideline)

verywellhealth.com, everypixel.com, dreamstime.com

Clinical Trials

CTA-CTN regulatory roadmap

While a CTA submission may be made in parallel to the Institutional Review Board (IRB) submission, a CTN submission should only be made after receiving IRB approval.



https://www.hsa.gov.sg/clinical-trials

Clinical Trials

The table below compares the differences between CTA and CTN:

	CTA	CTN
When does it apply	A trial investigating one or more locally unregistered therapeutic products or Class 2 CTGTPs, or unapproved use of a locally registered product.	A trial of locally registered therapeutic products or Class 2 CTGTPs used in accordance with their local approved labels.
Turn-around-time	30 working days, or 15 working days for Phase 1 trials solely to evaluate bioequivalence, bioavailability, food effect or drug-drug interactions. 60 working days for Class 2 CTGTP trials.	5 working days.

Clinical Trial Authorisation (CTA) | Clinical Trial Notification (CTN)

Documents required

- Clinical trial protocol
- Informed consent form (in English)
- Investigator's brochure for locally unregistered products
- Approved product label for locally registered products
- List of overseas trial sites (where applicable)
- Principal investigator's CV
- Good Manufacturing Practice (GMP) certificate
- Certificate of Analysis (COA) for study batches of investigational products
- Chemistry, Manufacturing and Control (CMC) information, when requested
- Documents for CRM Notification, if applicable:
  - List of components in a medical device system
  - Packing list for study-visits specific lab kits, if products in lab kits are not declared in application form

CTGTP webpage

Cell, tissue and gene therapy products

The new regulations for cell, tissue and gene therapy products in Singapore have taken effect from 1 March 2021.

CHECK REQUIREMENTS NOW →

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- Register of CTGTP
- CTGTP applications

https://www.hsa.gov.sg/ctgtp