Regulatory Update on Advanced Therapy Products in Hong Kong

Department of Health
The Government of the Hong Kong Special Administrative Region

August 2021

Content

- **What** is **ATP**?
- **Regulation** of ATP
  - **Pharmacy and Poisons** (**Amendment**) **Ordinance** 2020
- **Scope** of ATP Regulation
  - **Classification** of ATP
  - **Record Keeping**
  - **Labelling**
  - **Manufacture**
  - **ADR reporting**
  - **Import & Export**
  - **Product Registration**
  - **Clinical Trial**

What is Advanced Therapy Product?

- **ATPs*** are **innovative** medicinal products based on **genes**, **cells** and **tissues**
- **Scientific advancement** in ATP may offer **great medical potential**
- **Risks** and **long-term side effects** need to be carefully managed due to their **complicated nature** and the **limited knowledge** about these products

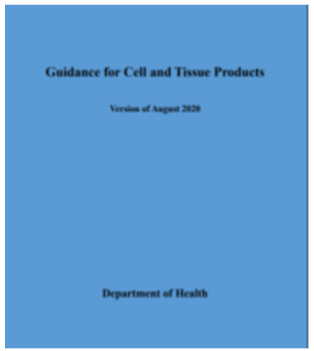
* The exact legal definition of “Advanced Therapy Product” is set out in the section 2 of the Pharmacy and Poisons Ordinance (Cap. 138), which is available at https://www.elegislation.gov.hk

Regulation of Cells & Tissues Products

Risk-based Approach

Separate Regulatory Framework ⟵ ⟶ **Pharmaceutical Products under the PPO**

Low Risk	High Risk
Minimal	Substantial manipulation
Homologous use	Non-homologous use



Guidelines & Standards

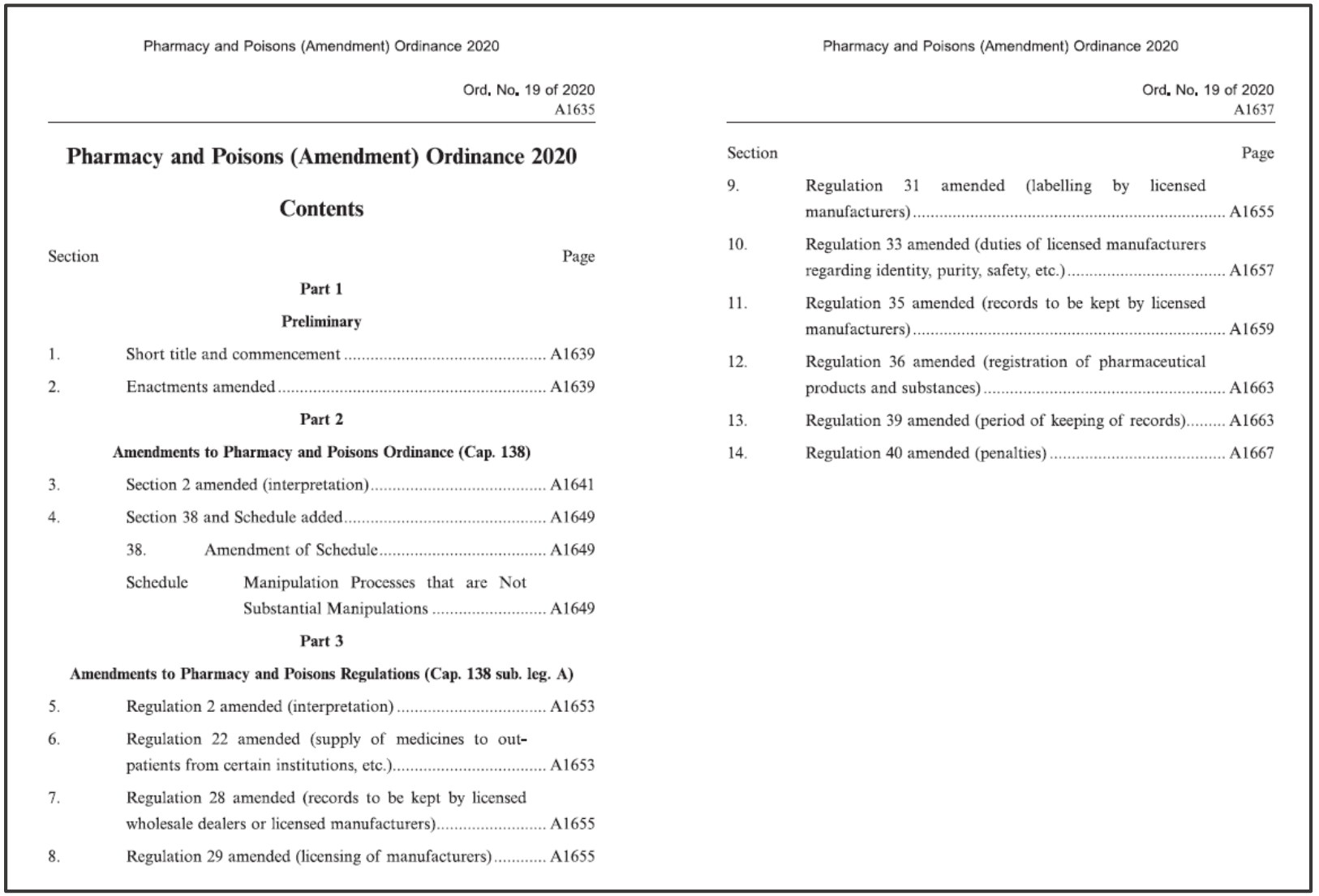
Cell and Tissue for Human Application

Advanced Therapy Products

- Somatic Cell Therapy Products
- Tissue Engineered Products
- Gene Therapy Products

Available at https://www.advancedtherapyinfo.gov.hk/cbb/en/doc/Guidance_for_Cell_and_Tissue_Products.pdf

Pharmacy and Poisons (Amendment) Ordinance 2020



Pharmacy and Poisons (Amendment) Ordinance 2020

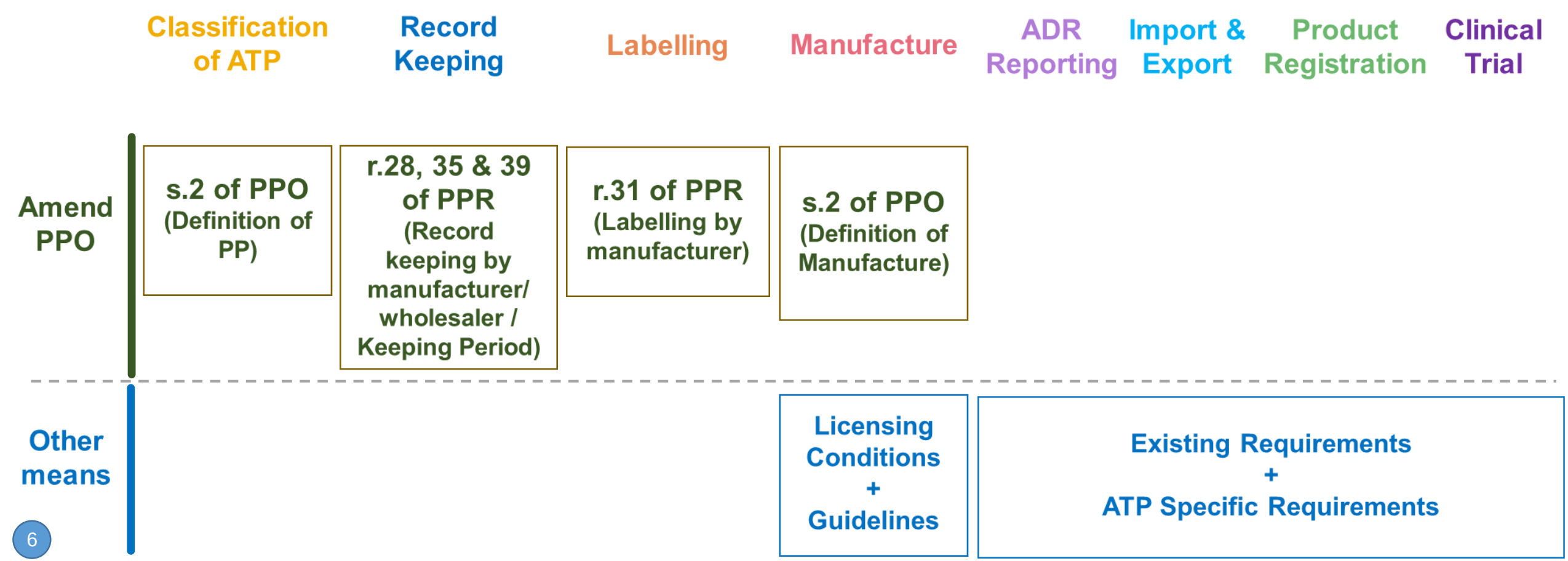
Contents

Amendment Ordinance

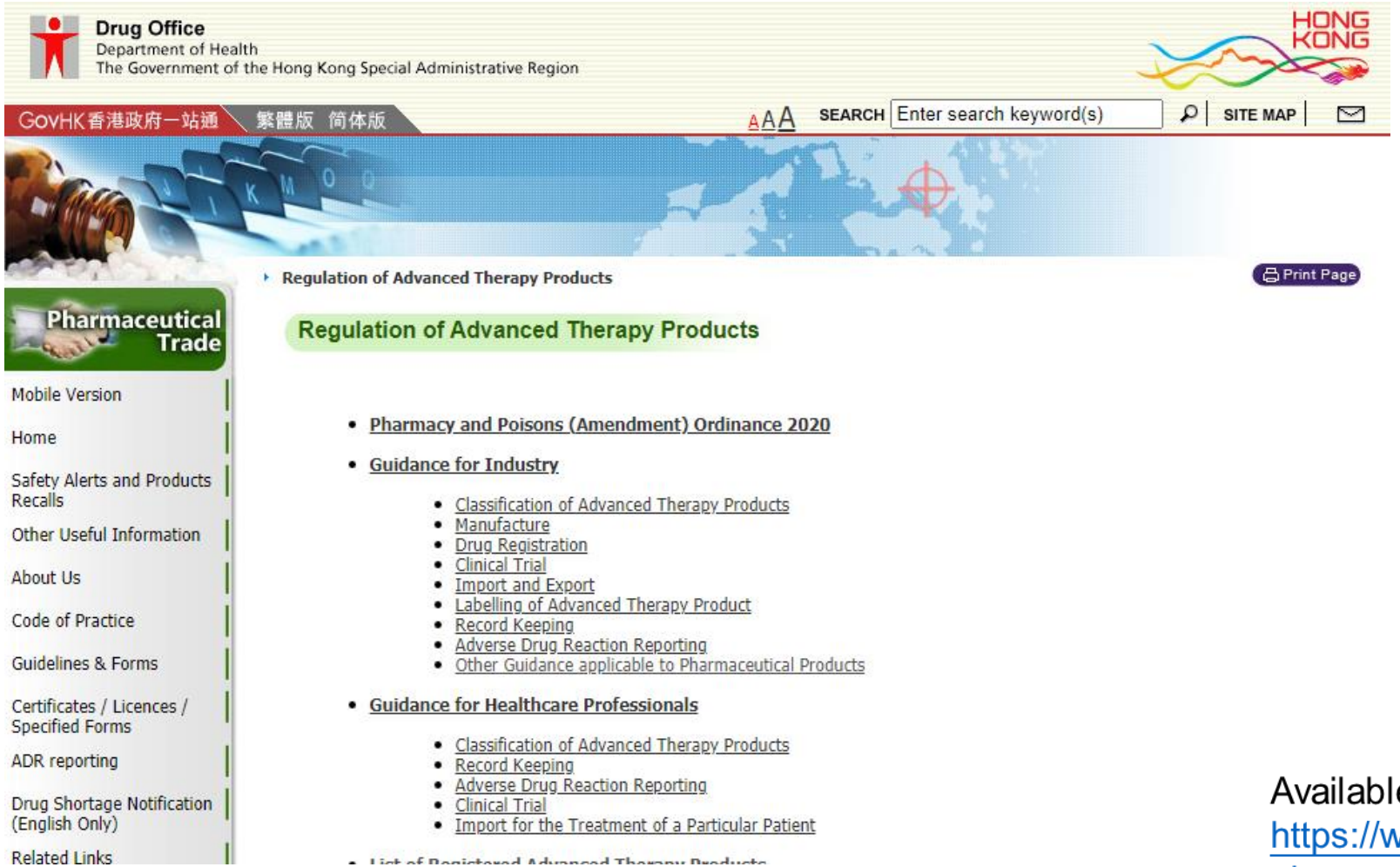
- **Amended Pharmacy and Poisons Ordinance** to regulate ATP
- **Passed** by **LegCo** and **gazetted** in **July 2020**
- **Come into operation** on **1 August 2021**

Available at
https://www.gld.gov.hk/egazette/pdf/20202430/es12020243019.pdf

Scopes of ATP Regulation



Relevant Guidance



Available at
https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

Classification of ATP

Classification of ATP

To include ATP in PP Definition (S.2)

Existing

pharmaceutical product (藥劑製品) and ***medicine*** (藥物) mean any substance or combination of substances—

(a) presented as having properties for treating or preventing disease in human beings or animals; or

(b) that may be used in, or administered to, human beings or animals, either with a view to—

(i) restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; or

(ii) making a medical diagnosis;

Amended Version

pharmaceutical product (藥劑製品)—

(a) means a substance or combination of substances that—

(i) is presented as having properties for treating or preventing disease in human beings or animals; or

(ii) may be used in or administered to human beings or animals with a view to—

(A) restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action; or

(B) making a medical diagnosis; and

(b) includes an advanced therapy product;

medicine (藥物) has the same meaning as in the definition of ***pharmaceutical product***;

Definition of ATP (S.2)

New **Provision**

”**Advanced therapy product**” (**先進療法製品**) means 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**;

Definition of Gene Therapy Product (S.2)

New **Provision**

Gene therapy product (基因療法製品)—

(a) means a product—

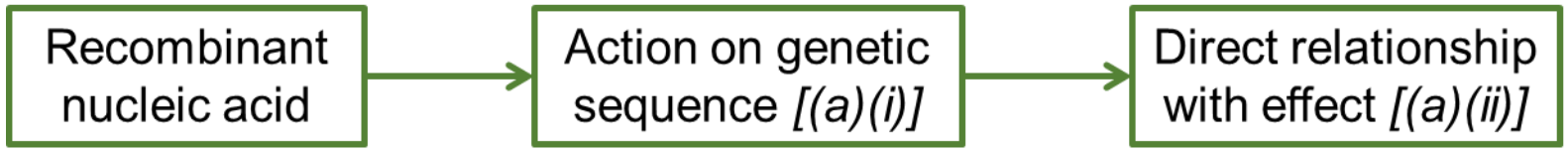
(i) that contains an active substance containing or consisting of a **recombinant nucleic acid** that may be used in or administered to human beings with a view to **regulating, repairing, replacing, adding or deleting** a **genetic sequence**; and

(ii) the **therapeutic**, **prophylactic** or **diagnostic effect** of which relates directly to—

(A) the recombinant nucleic acid **sequence** it contains; or

(B) the **product** of **genetic expression** of that sequence; but

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



Definition of Somatic Cell Therapy Product (S.2)

New **Provision**

Somatic cell therapy product (體細胞療法製品) means a product that—

(a) 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;

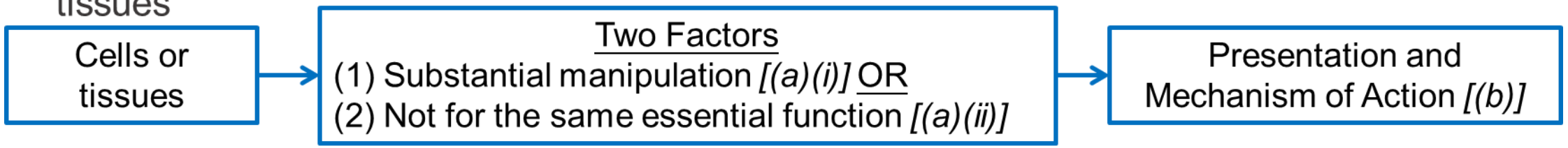
(ii) cells or tissues that are **not intended to be used for the same essential functions** in their recipient as in their donor; and

(b) 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



Definition of Tissue Engineered Product (S.2)

New **Provision**

Tissue engineered product (組織工程製品)—

(a) means a product that—

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

(A) 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;

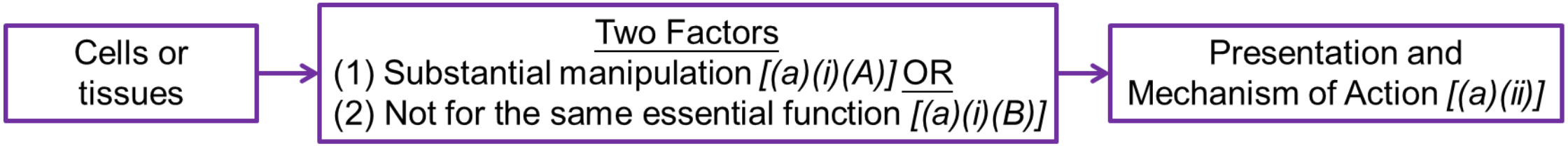
(B) cells or tissues that are **not intended to be used for the same essential functions** in their recipient as in their donor; and

(ii) 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—

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

(ii) does **not act principally by pharmacological**, **immunological** or **metabolic action**



Schedule for "Non-substantial" Manipulation

New **Provision**

S.2

substantial manipulation (實質處理), in relation to cells or tissues, does **not** include the manipulation processes **set out in the Schedule**;

Schedule

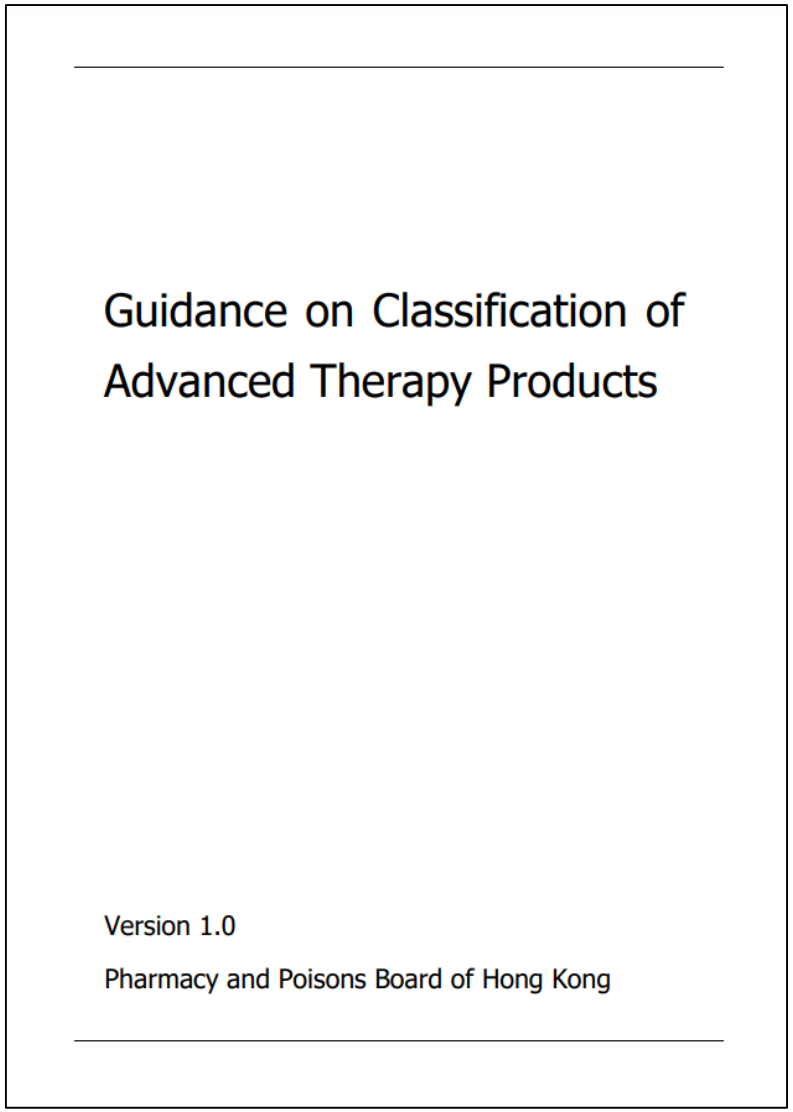
Manipulation Processes that are **Not Substantial Manipulations**

1. Cutting
2. Grinding
3. Shaping
4. Centrifugation
5. Soaking in antibiotic or antimicrobial solutions
6. Sterilization
7. Irradiation
8. Cell separation, concentration or purification
9. Filtering
10. Lyophilization
11. Freezing
12. Cryopreservation
13. Vitrification

S.38 Amendment of Schedule

The **Director of Health** may, by notice published in the Gazette, amend the Schedule.

Guidance on Classification of ATP


Guidance on Classification of Advanced Therapy Products

Version 1.0

Pharmacy and Poisons Board of Hong Kong

CONTENTS

Can be found at
https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

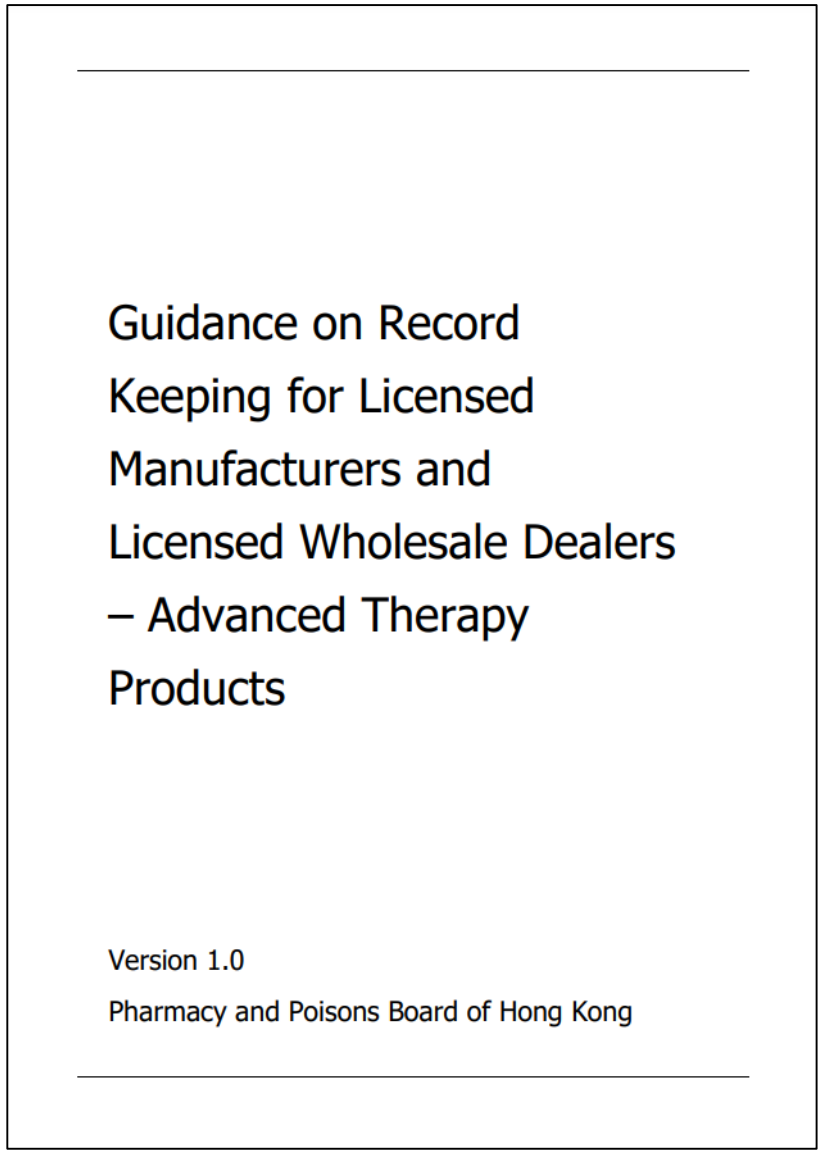
Record Keeping

Record Keeping

- Aim to ensure **traceability**
- To require retention of record on
  - **Distribution**
  - **Practitioner** responsible for use of product

  for **30 years** after expiry date
- Provisions for **bankruptcy/wound up/dissolution** and **cessation** of licence
  - Transfer specified documents to **Pharmacy and Poisons Board** within **specified timeframes**
- **Guidance** to **Medical Practitioners**, **Dentists** and **Institutions**

Guidance on Record Keeping for Licensed Manufacturers and Licensed Wholesale Dealers



Guidance on Record Keeping for Licensed Manufacturers and Licensed Wholesale Dealers – Advanced Therapy Products

Version 1.0

Pharmacy and Poisons Board of Hong Kong

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Record Keeping

Transaction Records by WDL and ML
(Section 5 of the Guidance)

- Required under regulation 28 of the PPR
- Record of particulars of **acquisition** (r. 28(1)) and **disposal** (r.28(2)) of PPs (including ATPs) and Poisons

(a) the date of the transaction;

(b) the name of the supplier;

(c) the name of the poison or pharmaceutical product;

(ca) the batch number, pack size and unit of quantity of the poison or pharmaceutical product;

(d) the total quantity of the poison or pharmaceutical product;

(e) the nature of the transaction; and

(f) a reference to the invoice or other documents supporting the transaction.

(a) the date of the transaction;

(b) the nature of the transaction;

(c) the name of the person to whom the poison or pharmaceutical product is supplied;

(ca) for an ATP supplied for use by a registered medical practitioner or registered dentist – the name and address of the practitioner or dentist;

(d) the total quantity of the poison or pharmaceutical product;

(e) a reference to the invoice or other documents supporting the transaction;

(f) the name of the poison or pharmaceutical product;

(fa) the batch number, pack size and unit of quantity of the poison or pharmaceutical product;

(g) the balance of the poison or pharmaceutical product remaining in his possession after the transaction.

- Same requirement as other PPs, except
  - **r. 28(2)(ca)** for **disposal** of **ATPs**
  - Duration – **30 years** after the expiry date of the product
  - **Transfer** to **the Board** if **cessation** of operation (Section 6 of the Guidance)

* ML should also refer to requirements in the GMP Guide if applicable.

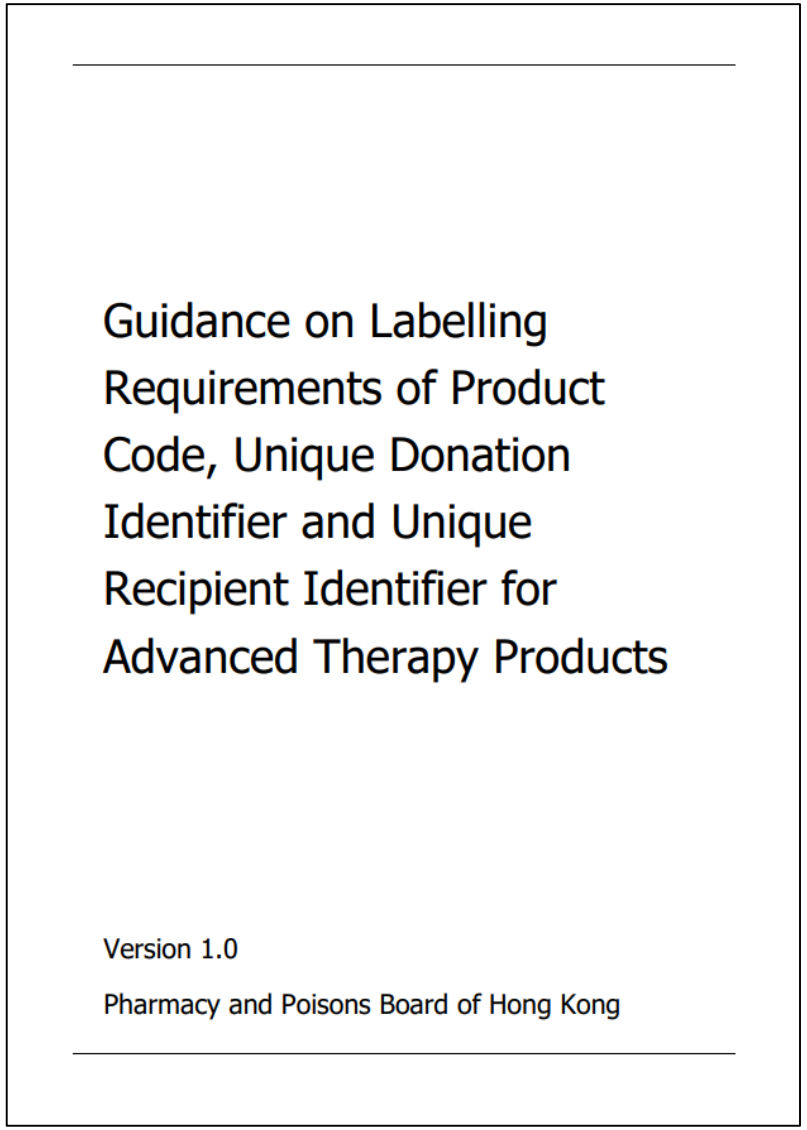
Labelling

Labelling

- **Labelling** of ATPs with
  - **Product code**
  - **Unique donation identifier (UDI)**
  - For **autologous** product
    - **Unique recipient identifier (URI)**
    - **“For autologous use only”** or **“只供自體使用”**
- Code and Identifiers assigned according to **Code of Practice**
- International recognized systems
  - **ISBT 128** standard
  - **S**ingle **E**uropean **C**ode (**SEC**)

Labelling

Guidance on Labelling Requirements of Product Code, UDI and URI for ATP



Guidance on Labelling Requirements of Product Code, Unique Donation Identifier and Unique Recipient Identifier for Advanced Therapy Products

Version 1.0

Pharmacy and Poisons Board of Hong Kong

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Can be found at
https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

Product Code & Unique Donation Identifier

- **Product Code**
  - Coding sequence for **identification** of **cell and tissue types** contained in an ATP
- **Unique Donation identifier (UDI)**
  - **Unique** sequence attributed to **specific donation** of cells or tissues for unique identification
- Two widely accepted coding systems for human cells and tissues
  - **ISBT 128** by ICCBBA
  - **Single European Code** (**SEC**) – for EU
  - Both systems include two components – **Product Code** + **UDI**
- For ATPs containing **human** cells or tissues
  - Either **ISBT 128** **or** **SEC** could be used to meet both the Product Code and UDI requirement
  - If **NOT**, assigned according to **section 4 (Product Code)** and **section 5 (UDI)** of the Guidance

Unique Recipient Identifier (URI)

- Applies **only** to ATPs for **autologous use***
- **Combination** of **recipient information** sufficient for healthcare professionals to **verify** the **identity** of the intended recipient
- URI should consist of at least **2 sets** of information

Recipient's **surname** followed by **initials** of first name

+

either

Month and **year** of **birth**

or

Number/sequence referring to the recipient
(e.g. part of recipient's hospital no. /medical record no.)

- Example:

Name of Recipient: ChanTM
Month and Year of Birth: 01/1960

- Should ensure HCP fully understand how to interpret and use the URI to verify the identity of the recipient
- Should comply with the Personal Data (Privacy) Ordinance (Cap. 486) requirements

* ATPs for autologous use should also be labelled with "**For autologous use only**" or "**只供自體使用**"

Manufacture

Manufacture

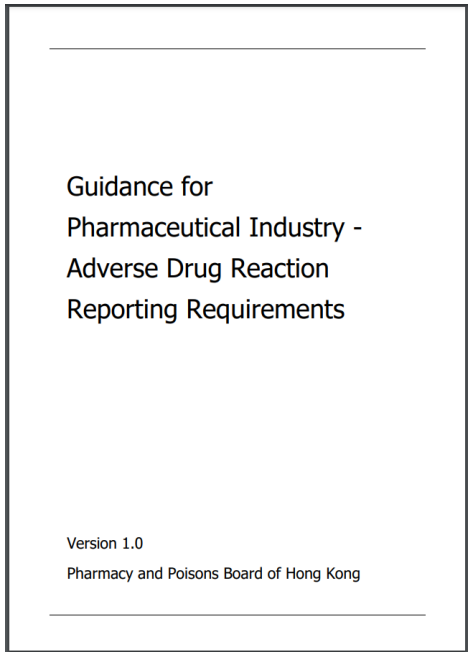
- **Manufacturing Licence** is required for **ALL** facilities
  - that involve **substantial manipulation** of cells or tissues in production process, including **institutions**
  - for the production of **GTP**
  - for **affixing** to the container of ATP a **label*** stating –
    - **Product code**
    - **Unique donation identifier (UDI)**
    - **Unique recipient identifier (URI)**
    - **"For autologous use only"** or **"只供自體使用"**

* Licence for Manufacturer (Secondary Packaging) if **only involves** labelling, re-labelling, cartoning, re-cartoning or adding additional information to PP which are already enclosed in the container in which they are to be sold or supplied.

ADR Reporting

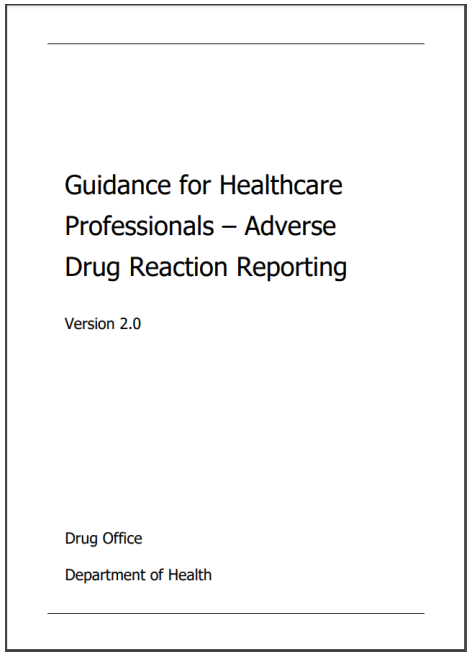
ADR Reporting

- **Existing** requirements to report ADR
- **Guidance** for **industry** & **HCP**
  - **Industry**
    - to **report** all **serious OR unexpected ADR**
  - **Traceability**
    - Include the **Batch number**
    - System in place capable of linking ADR reports with other traceability data
  - **List** of potential **ADR** of **concern**


Guidance for Pharmaceutical Industry - Adverse Drug Reaction Reporting Requirements

Version 1.0

Pharmacy and Poisons Board of Hong Kong


Guidance for Healthcare Professionals – Adverse Drug Reaction Reporting

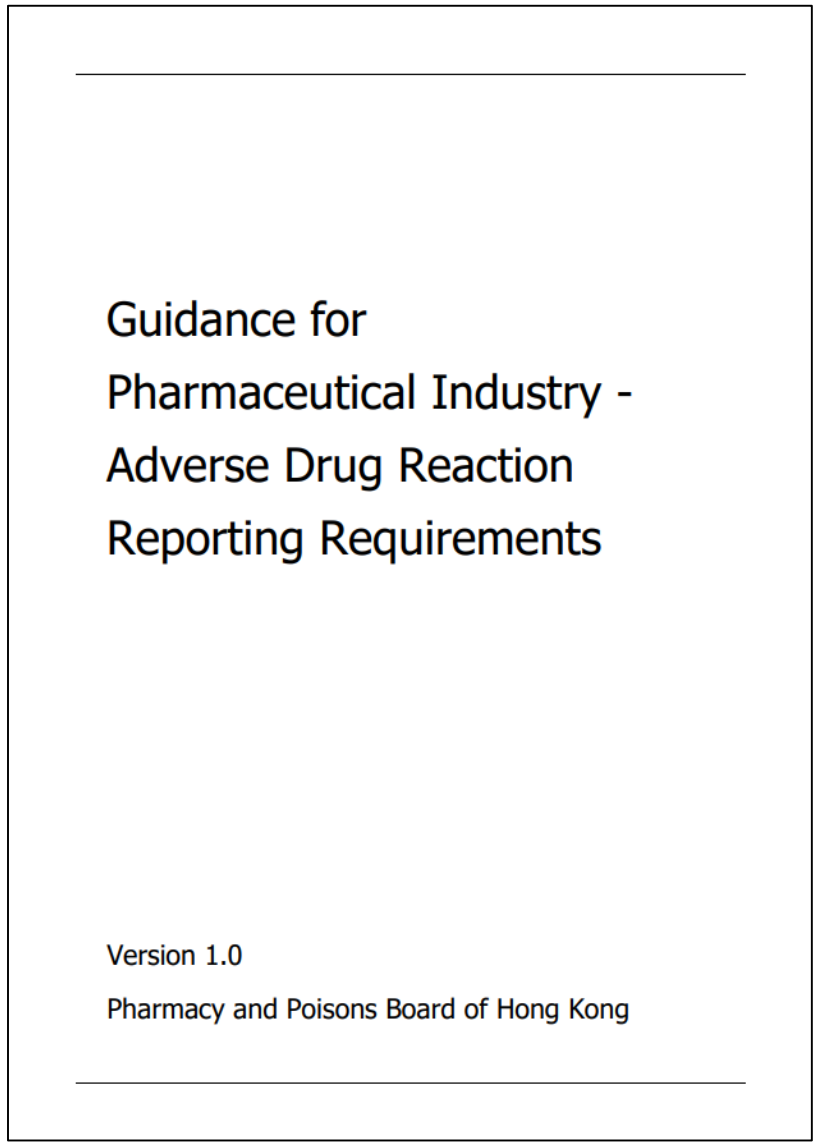
Version 2.0

Drug Office

Department of Health

ADR Reporting

Guidance for Pharmaceutical Industry – Adverse Drug Reaction Reporting Requirements



Guidance for Pharmaceutical Industry - Adverse Drug Reaction Reporting Requirements

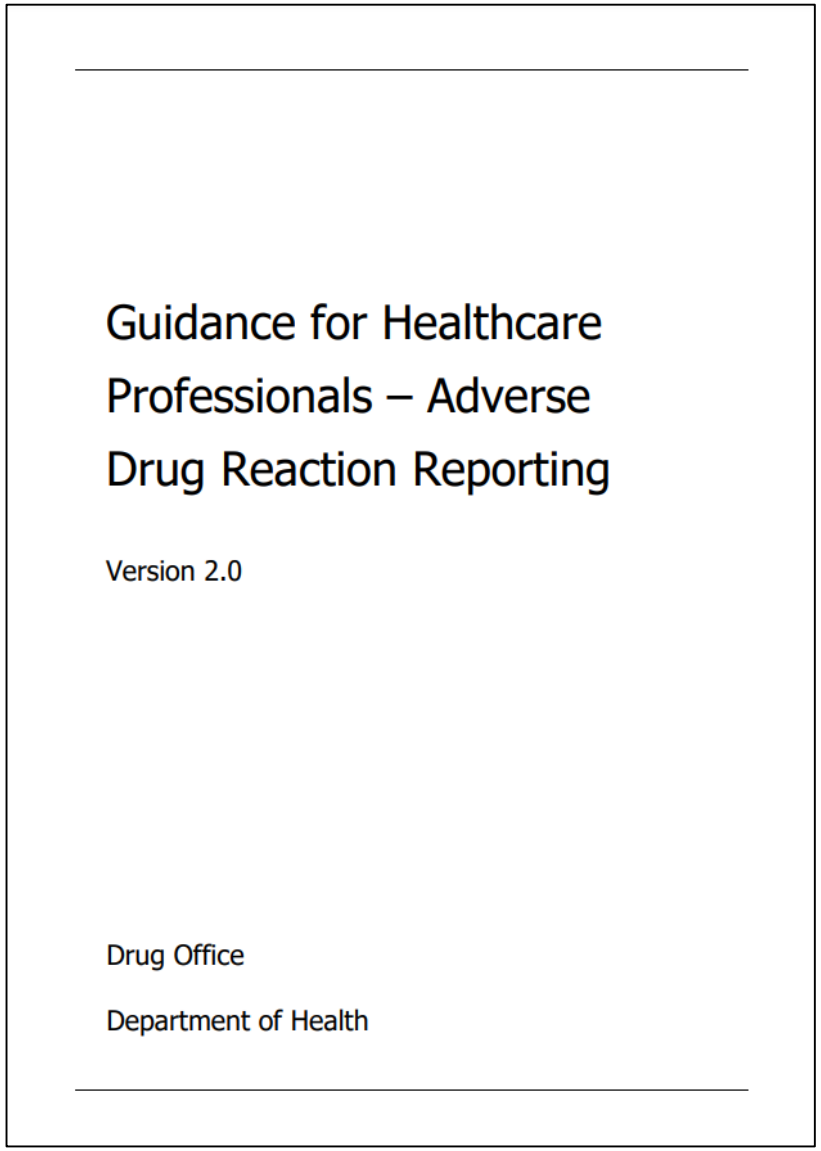
Version 1.0

Pharmacy and Poisons Board of Hong Kong

CONTENTS

ADR Reporting

Guidance for Healthcare Professionals – Adverse Drug Reaction Reporting

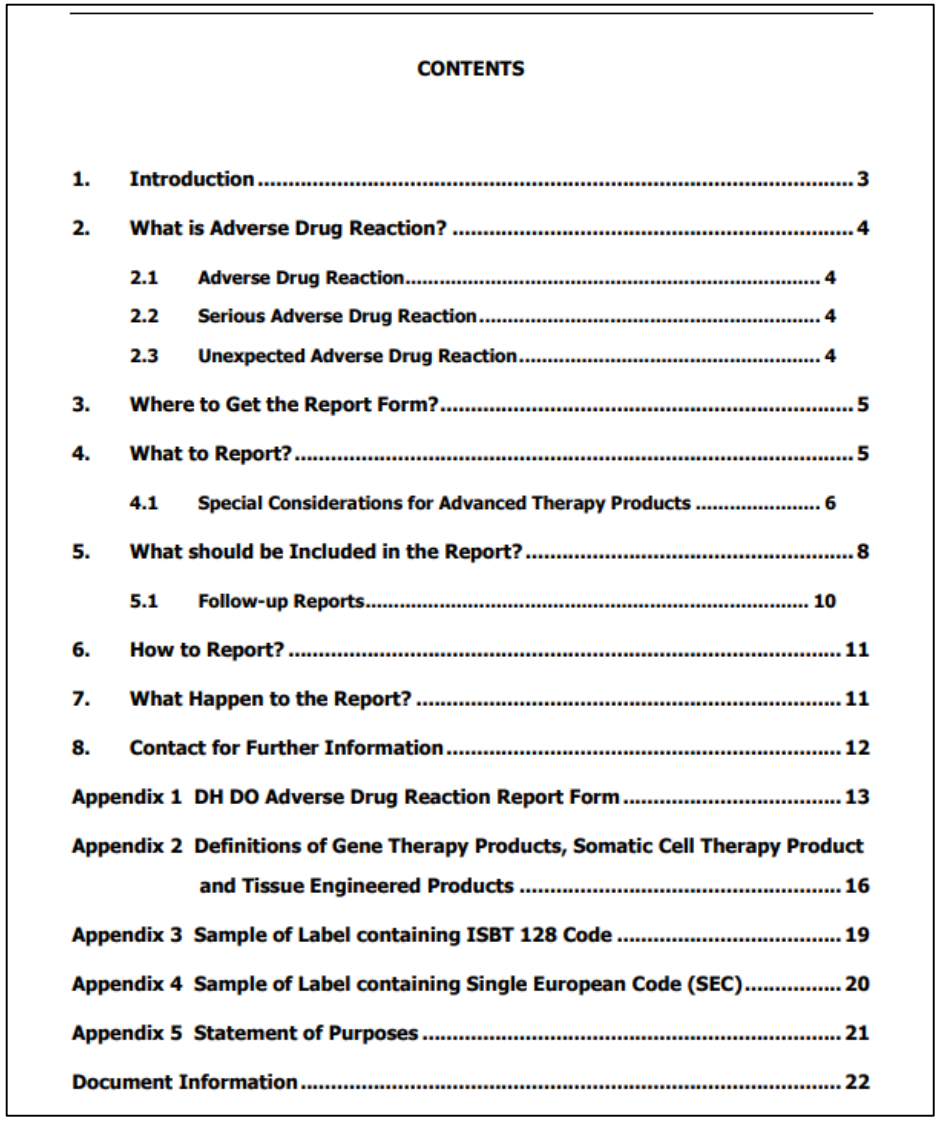


Guidance for Healthcare Professionals – Adverse Drug Reaction Reporting

Version 2.0

Drug Office

Department of Health



CONTENTS

Potential ADR of Concern
(Section 6.1 of the Guidance)

6.1 Potential Adverse Drug Reactions of Concern

Some potential adverse drug reactions of concern are listed below. Nevertheless, not all of the adverse drug reactions listed below are unique to ATPs. The list serves to provide examples to stimulate further considerations.

- adverse drug reactions related to quality characteristics of the product
  - transmission of diseases (e.g. viral, bacterial or parasitical infections and infestations) in relation to the origin of cells or tissues
  - tumourigenesis due to the alteration of differentiation capacity of the cells during the manufacturing process, "off target" mutations and unintended "on target" mutations in relation to gene editing, etc.
- adverse drug reactions related to the storage and distribution of the product
  - treatment failure due to impact on the biologic activity in related to preservation, freezing and thawing and breaking the controlled temperature conditions
- adverse drug reactions related to patient associated conditions/disease or underlying disease, or concomitant treatment/ interactions with other medicinal products
  - unwanted immunogenicity and the consequences
  - adverse drug reactions related to conditioning of patient, e.g. chemotherapy in case of CAR T-cell therapy
  - adverse drug reactions related to both intended and unintended genetic modification of the patient's cells
  - early and late consequences of homing, grafting, differentiation, migration and proliferation
  - infection with vectors used in gene therapy medicinal products
  - adverse drug reactions related to clinical follow-up, e.g. immunosuppression associated with the co-medication
- adverse drug reactions related to reconstitution procedures
  - dosing errors and maladministration
- adverse drug reactions related to administration procedures and re-administration
- adverse drug reactions related to persistence of the product in the patient
  - later complications (e.g. malignancies and autoimmunity)
  - adverse drug reactions related to non-specific integration into other cells with the potential of tumourigenicity
  - adverse drug reactions related to germ line integration of transgene or other genetic transformation of the germ line
- transmission of virus or vector to healthcare professionals, care givers, offspring and other close contacts
- adverse drug reactions occurring in offspring due to:
  - foetal transmission of vectors, biologically active substances, cells, infectious agents, etc.
  - transmammary exposure of children for lactating women (to vectors, biologically active substances, cells, infectious agents, etc.)

Import & Export

Import/Export

- **Same** requirements as other **pharmaceutical products** + **Considerations** specific to **ATPs**
- Requires an **Import/Export licence** to import/export of pharmaceutical products
  - Under the Import and Export Ordinance, (Cap. 60)
- Person carrying on **business** as an **importer** or **exporter** of PP –
  - **Licensed wholesale dealer** or
  - **Licensed manufacturer** (import for own manufacturing or export of own manufactured product)

Import/Export

Guidance on Application of Import and Export Licences

Guidance on Application of Import and Export Licences – Advanced Therapy Products

Version 1.0

Drug Office

Department of Health

CONTENTS

Can be found at https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

Scope of the Guidance

- **Registered** ATPs
- **Unregistered** ATPs for –
  - Clinical Trial ← Same as other PPs – Requires a certificate for clinical trial/medicinal test
  - Treatment of a particular patient
  - Re-export ← Same as other PPs
- **Starting** and **raw materials** for ATP **manufacturing**
- **Other relevant legislations**

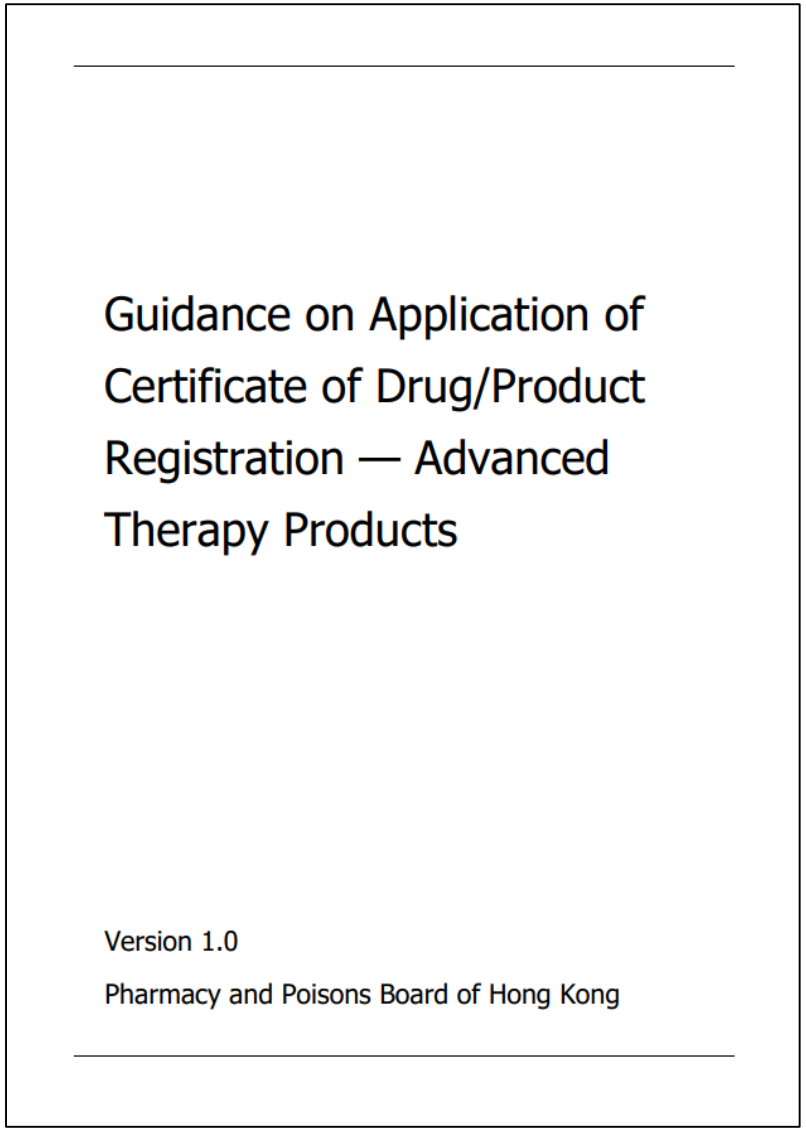
Other relevant Legislation
(Section 9 of the Guidance)

Subject Matter	Materials	Examples	Legislation	Responsible Department/ Office	Website
Infectious agents	Biological materials containing or consisting of or suspected to be containing of infectious agents (e.g. viral vectors)	Viral Vector	Prevention and Control of Disease Regulation (Cap. 599A)	**Port Health** Division of Department of Health	https://www.dh.gov.hk/english/main/main_ph/main_ph.html
Animal Products (Rabies)	Materials containing or consisting of parts or derivative of a dog, a cat or any animal that has been infected with rabies	Dog skin, canine plasma	Rabies Regulation (Cap. 421A)	Agriculture, Fisheries and Conservation Department (**AFCD**)	https://www.afcd.gov.hk/english/quarantine/qua_ie/qua_ie.html
Genetically Modified Organisms (**GMO**)	Starting and raw materials containing or consisting of GMOs ** Not applicable to GMO that is a PP for use by human being*	GM viral vector	Genetically Modified Organisms (Control of Release) Ordinance (Cap. 607)		https://www.afcd.gov.hk/english/conservation/con_gmo/con_gmo.html

Product Registration

Product Registration

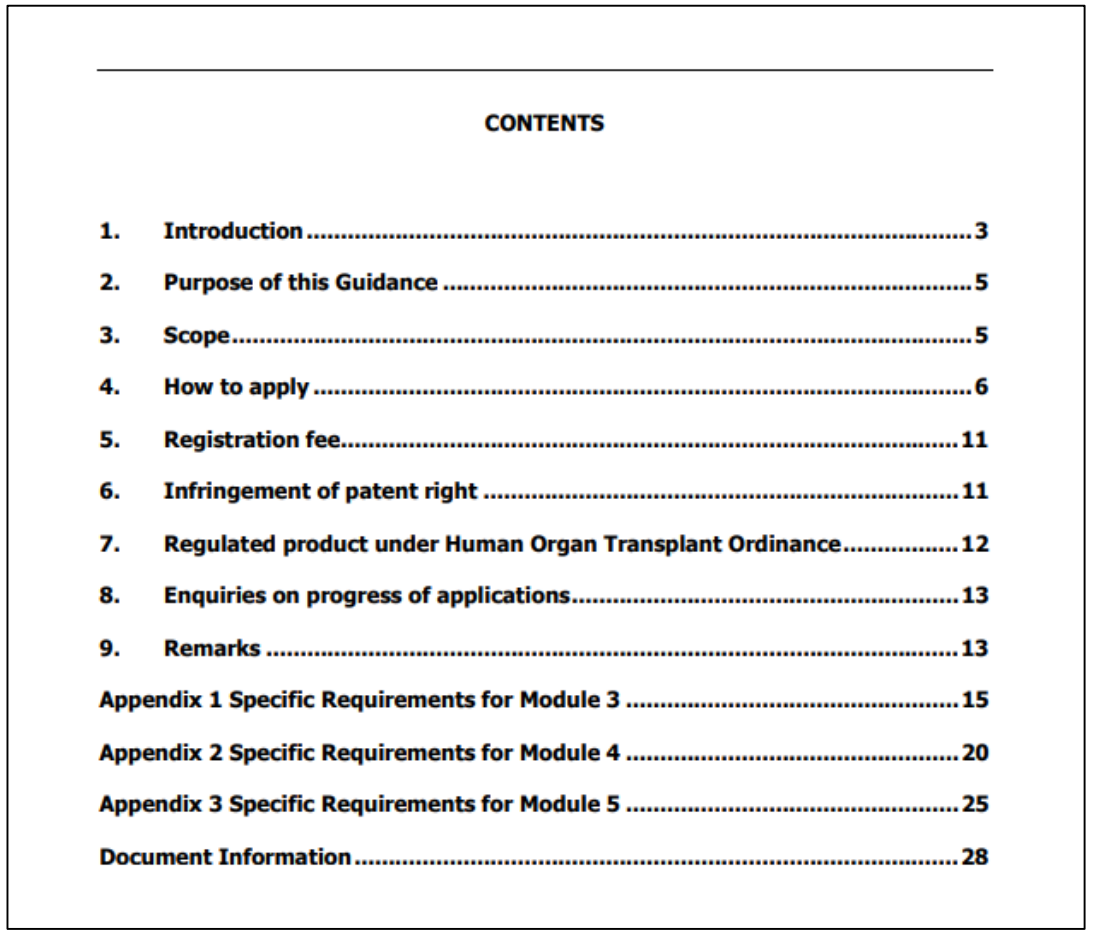
Guidance on Application of Certificate of Drug/Product Registration



Guidance on Application of Certificate of Drug/Product Registration — Advanced Therapy Products

Version 1.0

Pharmacy and Poisons Board of Hong Kong



CONTENTS

Can be found at
https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

Product Registration

Requirements specific to ATPs

- Registration **approval** of the product in **two or more** of the following countries* –
  - Australia, Austria, Belgium, Bulgaria, Canada, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Holland, Hungary, Ireland, Italy, Japan, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, UK and USA

  * Approval from the **EU countries** must be issued from **EMA**
- Submission of **ICH CTD Modules 2 – 5**
  - **Specific requirements** to ICH CTD Modules 3 (Quality), 4 (Nonclinical) and 5 (Clinical) in **Appendices 1 – 3** of guidance
- Description of **traceability system**
  - Bidirectional traceability from donor to medical practitioner/dentist using the ATP and vice versa
- Product **label**
  - Should comply with "***Guidance*** *on Labelling Requirements of* ***Product Code***, ***Unique Donation Identifier*** *and* ***Unique Recipient Identifier*** *for ATPs*"
  - Should **specify** the **coding system** adopted

Regulated Product under HOTO

- "**Organ**" is subject to the regulatory control under **Human Organ Transplant Ordinance** (Cap. 465) (**HOTO**), including the **prohibition** of **commercial dealings**.
- 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 **certain criteria** have been met.

Section 7A of HOTO

Regulated product (受規管產品) means a product containing any structured arrangement of tissues that—
(i) falls within paragraph (a)(iii) of the **definition of organ** in section 2; and
(ii) has been **subjected to processing**.

Section 7A of HOTO

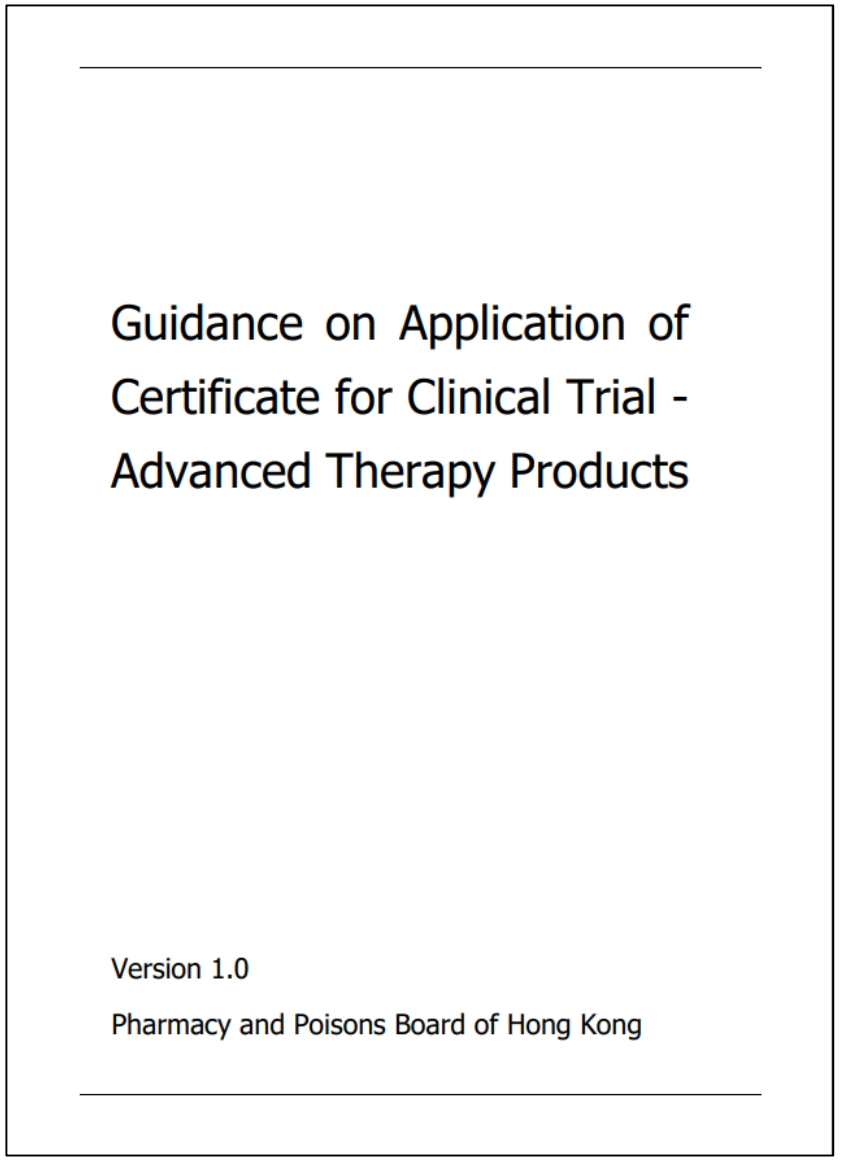
Processing (加工處理), in relation to any structured arrangement of tissues, means any **activity** performed on the tissues which **alters** the **biological characteristics**, **function** or **integrity** of the **tissues**, but does not include recovering or preparing the tissues, preserving the tissues for storage, or removing the tissues from storage.

- If an **ATP** falls within the definition of "**regulated product**" in HOTO, the application **dossier for exemption** may be submitted to **Drug Office** together with **product registration**.
- For details of application for exemption of **regulated product**, please refer to DH website.
  - https://www.dh.gov.hk/english/useful/hot_exemption.html

Clinical Trial

Clinical Trial

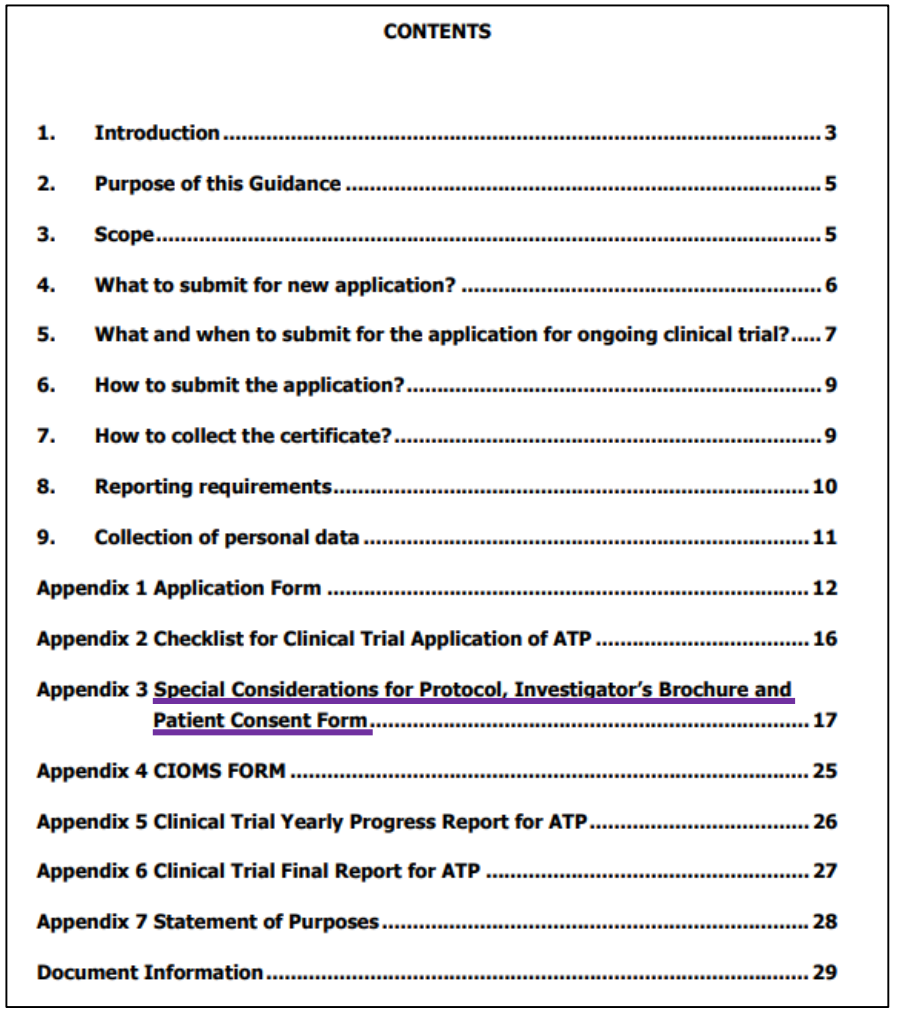
Guidance on Application of Certificate for Clinical Trial



Guidance on Application of Certificate for Clinical Trial - Advanced Therapy Products

Version 1.0

Pharmacy and Poisons Board of Hong Kong



CONTENTS

Can be found at
https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

Clinical Trial

Considerations specific to ATPs

- **Traceability**
  - Ensure **bidirectional** traceability **from donor to subject** and **from subject to donor**
  - **Sponsor** should –
    - Ensure that the **manufacturer** has set up a **system** that enables bidirectional tracking of cells or tissues contained in ATPs
    - Provide the **investigator** with detailed **instructions** to ensure traceability
  - Data should be kept for **30 years** after the expiry date of the product
- **Informed consent**
  - Where applicable, **subject** should be **informed** of –
    - Irreversible nature of ATP
    - Risk to close contacts and off-springs
    - If the treatment could compromise future pregnancies
    - The need for long-term follow-up and seeking subject commitment
- **Long-term follow-up**
  - **Scheme** for long-term follow-up where applicable

Thank You