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

Version 1.0.1
(Draft for comment)

Drug Office

Department of Health

Contents

1. Introduction

1.1 In Hong Kong, Advanced Therapy Products ("ATPs") are regulated as pharmaceutical products under the Pharmacy and Poisons Ordinance, Cap. 138 ("PPO").

1.2 Under the PPO, "pharmaceutical product"—

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

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

(2) 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.

1.3 "Advanced Therapy Product" 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.

1.4 Definitions of gene therapy product, somatic cell therapy product and tissue engineered product are appended at Appendix 1.

1.5 According to Regulation 36B of the Pharmacy and Poisons Regulations (Cap. 138A), a person must not conduct a clinical trial on human beings, or cause or permit such a trial to be conducted, except in accordance with a valid clinical trial certificate issued by the Pharmacy and Poisons Board (the Board).

1.6 The Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (the Committee) is established under the Board to issue the certificate. The Drug Office of Department of Health (DH DO) is the executive arm of the Committee.

1.7 The Committee adopted the definition of "clinical trial" given in the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP) which is defined as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy".

2. Purpose of this Guidance

2.1 This guidance outlines the requirements and procedures for the application of certificate for clinical trial of ATP.

2.2 In addition, this guidance also highlights some special considerations for selected documents required for application of certificate for clinical trial of ATP.

3. Scope

3.1 This guidance applies to applicants for the certificate for clinical trial of ATP.

3.2 Applicant could be:

(a) sponsor[1] of a clinical trial or a local company, which holds relevant licence(s) (e.g. wholesale dealer licence, antibiotic permit, where applicable) who can handle ATPs;

(b) sponsor-investigator[2] who initiates and conducts a clinical trial;

(c) principal investigator who conducts a clinical trial.

[1]Sponsor means an individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

[2]Sponsor-investigator means an individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

4. What to submit for new application?

4.1 The following documents are required for the application:

- A completed application form (appendix 2).
- A completed checklist (appendix 3).
- A cover letter listing all the submitted documents and including a brief summary of the ATP on the following (but not limited to):
  - (a) proposed indication(s) and mode of action(s);
  - (b) preclinical and clinical experience;
  - (c) anticipated risk(s) and clinical safety monitoring;
  - (d) rationale for design of the trial and determination of the dose range.
- A letter from the principal investigator confirming his involvement in the clinical trial.
- The Curriculum Vitae of the principal investigator.
- Documentary evidence proving that the clinical trial has been approved by the Ethics Committee of the institution where it will be conducted (this may be submitted when available at a later date).
- The proposed patient information and the patient consent form*, in both English and Chinese, or in Chinese only.
- A copy of the proposed protocol* for the clinical trial.
- Information of the ATP (e.g. investigator's brochure [IB]*, package insert, other information if applicable, etc.).
- A sample certificate of the analysis of the ATP.
- Evidence proving that the ATP is manufactured in accordance with Good Manufacturing Practices (GMP) (e.g. copy of GMP certificate of the ATP manufacturer).

** Please refer to appendix 4 for special considerations for patient consent form, protocol and investigator's brochure. Please also take references to the relevant information in the ICH Harmonised Guideline for GCP (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf)*

4.2 The following additional documents are required for studies which are also the subject of an application for approval by the National Medical Products Administration (NMPA):

- Drug clinical trial approval document (藥物臨牀試驗批件) issued by NMPA (this may be submitted when available at a later date).
- A copy of the protocol submitted to NMPA.

4.3 The above lists of documents are not exclusive. The applicant may be required to submit additional or updated documents to support the application. Documents may be submitted in electronic format in a CD-ROM, in addition to the paper copy.

5. What and when to submit for the application for ongoing clinical trial?

- All documents listed under section 4.
- A copy of the previous certificate.
- Clinical trial progress report(s) (if not available, please provide justification; if the trial has not been started, please also provide justification).

In order to avoid interruption of the ongoing clinical trial, applicants are advised to submit a new application **not later than 4 months** before the expiry of the current CTC. Late submission of application and/or provision of incomplete information may cause delay in issue of CTC.

[Important Note: According to Regulation 36B of the Pharmacy and Poisons Regulations (Cap. 138A), a person must not conduct a clinical trial on human beings, or cause or permit such a trial to be conducted, except in accordance with a valid clinical trial certificate issued by the Pharmacy and Poisons Board. Any person who contravenes the above commits an offence and is liable to a fine at level 2 (currently is HK$5,000).]

6. How to submit the application?

6.1 The applicant should submit the completed application form together with the relevant documents indicated in the document checklist to the Drug Evaluation and Import/Export Control Division, DH DO by:

- email to ct@dh.gov.hk; or
- mail or in person to the below address:

Address:	Office Hours:
Drug Evaluation and Import/Export Control Division, Drug Office, Department of Health, Suites 2002-05, 20/F, AIA Kowloon Tower, Landmark East, 100 How Ming Street, Kwun Tong, Kowloon Tel.: 3974 4175	Monday to Friday 9:00 a.m. to 1:00 p.m. 2:00 p.m. to 5:45 p.m. (up to 6:00 p.m. on Monday) (Shroff closes at 15 minutes earlier than the office hours) *(Closed on Saturdays, Sundays & Public Holidays)*

6.2 It will be acknowledged by receipt upon payment of the application fee (currently HK$1,420). If payment is made by cheque, the cheque should be made payable to "The Government of the Hong Kong Special Administrative Region" or "The Government of the HKSAR" and crossed. The acknowledgement receipt will contain an application number and the applicant may quote it when making an enquiry regarding the application.

7. How to collect the certificate?

When the application is approved, the applicant will be notified in writing. Payment of the certificate fee (currently HK$1,420) and collection of certificate should be made in person at the Drug Evaluation and Import/Export Control Division of Drug Office during office hours. If payment is made by cheque, the cheque should be made payable to "The Government of the Hong Kong Special Administrative Region" or "The Government of the HKSAR" and crossed.

8. Reporting requirements

All certificate holders of clinical trial of ATP are required to report to this office the following:

8.1 All local drug-related safety reports i.e. reports on adverse drug reactions (ADRs).

(a) For adverse drug reactions that are both serious* and unexpected** as soon as possible. (The attached CIOMS form [Appendix 5] may be used for reporting.)

(i) Fatal or life-threatening unexpected ADRs should be reported as soon as possible but no later than 7 calendar days after first knowledge by the sponsor that a case qualifies, followed by as complete a report as possible within 8 additional calendar days. This report must include an assessment of the importance and implication of the findings, including relevant previous experience with the same or similar medicinal products.

(ii) Other serious, unexpected ADRs that are not fatal or life-threatening, it should be reported as soon as possible but no later than 15 calendar days after first knowledge by the sponsor that the case meets the minimum criteria for expedited reporting.

* *Serious Adverse Drug Reaction or Adverse Event:*

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose: results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

** *Unexpected Adverse Drug Reaction:*

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational medicinal product).

(b) For non-serious adverse reactions and serious adverse reactions that are expected, it should be reported in a brief summary at the conclusion of the trial.

(c) For further details on ADRs reporting, please refer to the ***Guidance for Pharmaceutical Industry – Adverse Drug Reaction Reporting Requirements*** (http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/adr_reporting/index.html).

8.2 Progress report on yearly basis and a final study report at the end of the study. The attached forms specific to ATP (Appendix 6 & 7 respectively) may be used for reporting.

8.3 Please forward all reports to the following address:

Drug Evaluation and Import/Export Control Division, DO DH
Suites 2002-05, 20/F, AIA Kowloon Tower
Landmark East, 100 How Ming Street
Kwun Tong, Kowloon
Hong Kong
(Fax no.: 2803 4962)

9. Collection of personal data

Regarding the collection of personal data, please refer to "Statement of Purposes" at Appendix 8 for more information.

Appendix 1 Definitions of Advanced Therapy Products (Proposed)

Gene Therapy Product

Gene therapy product—

(a) means a product—

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

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

(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.

Somatic Cell Therapy Product

Somatic cell therapy product means a product that—

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

(1) 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;

(2) 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—

(1) treating, preventing or diagnosing a disease; or

(2) restoring, correcting or modifying physiological functions,

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

Tissue Engineered Product

Tissue engineered product—

(a) means a product that—

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

(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

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

(b) does not include a product that—

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

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

Substantial Manipulation

Substantial manipulation, in relation to cells or tissues, does not include the manipulation processes set out in the Schedule of the Pharmacy and Poisons Ordinance (Cap. 138).

Under the Schedule of Cap. 138, the following manipulation processes 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

Appendix 2 Application Form

Application for Certificate for Clinical Trial of Advanced Therapy Products

PART A: STUDY INFORMATION				
A1.	Protocol title		Protocol no.	
			Protocol date	
A2.	Name of applicant			
A3.	Business address of applicant		Tel. no.	
			Fax no.	
A4.	Name of principal investigator			
A5.	Name and address of institution conducting the study			
A6.	Is this a study in which a certificate was issued previously and will soon expire? ☐ Yes (CTC no._____ and valid until_____) ☐ No			
A7.	Is this study also the subject of an application for approval by the National Medical Products Administration (NMPA)? ☐ Yes (if available, the number of Drug Clinical Trial Approval Document (藥物臨牀試驗批件號)_____and date of approval_____) ☐ No			

PART B: STUDY DESCRIPTION		
B1.	The study is	☐ single centre ☐ multi-centre
B2.	No. of study centres in Hong Kong	Total no. of centres_____ Centre name(s)_____
B3.	Study centres outside Hong Kong (if any)	No. of centres in each country (e.g. Mainland China – 2 centres, Singapore – 2 centres)_____
B4.	Sponsor of the study	☐ the sponsor is a pharmaceutical company or research organisation/institution Name of sponsor: _____ Address of sponsor:_____ ☐ the study is initiated and conducted by a sponsor-investigator Name of sponsor:_____ Address of sponsor:_____ *(Remarks: As this study is initiated and conducted by a sponsor-investigator, the sponsor should be the same person as the applicant)*
B5.	Recruitment size	Planned no. of subjects in Hong Kong_____ Total planned no. of subjects world-wide_____
B6.	Study period	Planned start date_____ and planned end date_____
B7.	The study is	☐ phase I (first-in-man? ☐Yes ☐No) ☐ phase II ☐ phase III ☐ phase IV Describe if necessary:_____
B8.	The study is	☐ open label ☐ single blind ☐ double blind ☐ other (please specify)_____)
B9.	The study is	☐ non-randomized ☐ randomized
B10.	Therapeutic area	(e.g. Oncology, Haematology)
B11.	Disease/Disease type	(e.g. Prostate cancer, Haemophilia A)

PART C: STUDY DRUG				
C1.	ATP to be investigated			
	Name of ATP	ATP type: (GTP / SCTP / TEP)[1]	Strength[2]	Manufacturer
		☐ ☐ ☐		
		☐ ☐ ☐		
C2.	The study involves concurrent use of	☐ placebo ☐ concomitant drug (please fill in C5)	☐ comparator drug ☐ ATP (please fill in C3) ☐ Non-ATP (please fill in C4) ☐ none of the above	
C3.	ATP comparator used (if any)			
	Name of ATP	ATP type (GTP / SCTP / TEP)[1]	Strength[2]	Manufacturer
		☐ ☐ ☐		
		☐ ☐ ☐		
C4.	Non-ATP comparator used (if any)			
	Name of drug	Strength[3]	Manufacturer	
C5.	Concomitant drug used (if any)			
	Name of drug	Strength[3]	Manufacturer	

[1] GTP: Gene therapy product
SCTP: Somatic cell therapy product
TEP: Tissue engineered product

[2&3] Examples for Strength:

For ATP:

- Dispersion for infusion e.g. 2-16 million cells/2mL (total amount in total volume)
- Solution for injection e.g. 3×10^{12} genome copies/vial (total amount in a vial)

For non-ATP:

- Solution for injection e.g. 5mg/5ml (total amount in total volume)
- Powder for reconstitution e.g. 5mg/vial (total amount in a vial)
- Oral dosage form e.g. 100mg/tab

PART D: DECLARATION OF THE APPLICANT	
I/We* hereby declare that, if the application is approved and the study proceeds:	
D1.	Agree to submit local drug related safety reports, yearly progress reports and final study report of the study as stated in "Guidance on Application of Certificate for Clinical Trial – Advanced Therapy Products".
D2.	This study will be conducted in accordance with the principles established in Good Clinical Practice.
D3.	The information given in this application is true and correct.

* Delete as appropriate

Signature

Company stamp (if the applicant is a company)

Signatory's name in block letters

Date (DD/MM/YY)

PART E: FOR OFFICE USE ONLY	
Date Received	Fee Paid

Appendix 3 Checklist for Clinical Trial Application of ATP

(a) For all studies:		Yes	No
1.	A completed application form and this checklist.	☐	☐
2.	A cover letter listing all the submitted documents and including a brief summary of the ATP.	☐	☐
3.	A letter from the principal investigator confirming his involvement in the clinical trial.	☐	☐
4.	The Curriculum Vitae of the principal investigator.	☐	☐
5.	Documentary evidence that the clinical trial has been approved by the Ethics Committee of the institution in which it is to be conducted (this may be submitted when available at a later date).	☐	☐
6.	The proposed patient information and patient consent form, in both English and Chinese, or in Chinese only.	☐	☐
7.	A copy of the proposed protocol for the clinical trial.	☐	☐
8.	Information of the ATP (e.g. investigator's brochure, package insert, other information if applicable, etc.).	☐	☐
9.	A sample certificate of analysis of the ATP.	☐	☐
10.	Evidence that the ATP is manufactured in accordance with Good Manufacturing Practices (GMP) (e.g. copy of GMP certificate of the manufacturer).	☐	☐
11.	Application fee (HK$1,420)	☐	☐
(b) For studies in which a certificate was issued previously and will expire, the following additional documents:			
12.	A copy of the previous certificate.	☐	☐
13.	Clinical trial progress report(s) (if not available, please provide justification; if the trial has not been started, please also provide justification).	☐	☐
(c) For studies which are also the subject of an application for approval by the National Medical Products Administration (NMPA), the following additional documents:			
14.	Drug clinical trial approval document (藥物臨牀試驗批件) issued by NMPA. (this may be submitted when available at a later date).	☐	☐
15.	A copy of the protocol submitted to NMPA.	☐	☐

Appendix 4 Special Considerations for Protocol, Investigator's Brochure (IB) and Patient Consent Form

- *Clinical Trial Design:* The design of clinical trials with ATPs should take into account the specific characteristics of these medicinal products, as well as the potential risks to subjects, investigator's team and others (e.g. offspring, close contacts). Various aspects of the trial should be duly considered. To take dosing as an example, early phase clinical trials should attempt to define the dose range to be used in the pivotal trial. A rationale for a dose definition based on published literature data requires a thorough analysis of the comparability between products, including on aspects relating to starting material and manufacturing process, as well as the characteristics of patient populations treated. A description and justification of the dosage should always be provided in the Protocol. In case of ATPs with complex dosing regimens, the IB should contain adequate explanations for the rationale to ensure an adequate level of understanding and compliance by the investigator and those involved in the clinical trial.

- *Non-clinical studies:* The rationale for the non-clinical development should be discussed and justified, including in cases where the sponsor considers that non-clinical studies are not feasible. Comprehensive information about the non-clinical development should be provided in the IB. A summary of findings from non-clinical studies that potentially have clinical significance and from other clinical trials that are relevant to the clinical trial should be provided in the Protocol.

- *Quality of investigational ATPs:* In general, investigational ATPs should comply with the Good Manufacturing Practice Guide issued by the Pharmacy & Poisons Board.

  The impact of the variability of donor or patient based starting material should be taken into consideration when defining release specifications for cell-based ATPs (e.g. cell numbers/range of cell numbers, transduction efficiency). In the autologous setting, consideration should be given to how the disease status of the patient impacts on the quality of the starting material and potential variability of the final drug product.

  When the investigational ATP requires reconstitution before it is administered to the subject, the sponsor should ensure that the detailed instructions of the reconstitution process (as validated by the manufacturer of the product) are transmitted to the sites

where the product is going to be administered. The instructions should be detailed and clear enough so as to avoid negative impacts on the quality of the product (e.g. it is generally expected that, when the reconstitution involves thawing, the rate of temperature change during thawing is described.) Likewise, when the reconstitution requires the use of solvents and/or other materials these should be specified or, as appropriate, provided by the sponsor. The reconstitution should be described in the IB. It is acceptable that the detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB. Where appropriate (i.e. in the case of complex reconstitution procedure), training should be provided to those involved in the reconstitution process.

- *Batch release:* If applicable, in some specific cases (e.g. due to the short shelf-life), ATPs may need to be released prior to all results of specification testing is available. This approach needs to be justified and supported by performed risk analysis. The procedure that is taken when out of specification test results are obtained after the release of the product need to be provided.

- *Information on the product:* The IB should provide comprehensive information on the risks of the product (based on existing knowledge), including risks associated with the administration procedure and/or upstream interventions on subjects, and information on short and long-term safety issues particular to ATPs such as infections, immunogenicity/immunosuppression and malignant transformation.

  Information should also be provided on the potential impact of previous or concomitant treatments (e.g. in case of gene therapy products, risks associated with prior infection /vaccination with related viruses), as well as the potential consequences of the investigational medicinal product for the patient in case he/she requires further treatments for the targeted disease (e.g. an immunoglobulin treatment later in life could impact on expression of the introduced gene by antibody interaction). Where appropriate, the risk of treatment failure should also be addressed.

  The IB should be updated with information on emerging issues, including changes to the reference safety information as appropriate. A substantial modification application should be submitted accordingly for any change that is likely to have a substantial impact on

the safety or rights of the subjects, or on the reliability and robustness of the data generated in the clinical trial.

- *Handling of the ATP:* Detailed information should be provided in the IB on the product handling, containment and disposal. It is acceptable that detailed instructions are laid down in a separate document available at the site (e.g. handling instructions and/or pharmacy instructions), which can be attached as Annex to the IB.

  The level of information should be commensurate to the risks. For example, in case of ATPs that contain infectious biological material, it is expected that detailed instructions for handling and disposal are provided. In case the ATP includes a bacterial or viral vector with the potential for shedding, the risks and precautionary measures should be clearly communicated to the subject and/or, as appropriate, to caregivers.

  Where necessary, information on risk minimisation measures to protect health care professionals that are involved in the handling of the medicinal product should also be provided.

- *Risk-minimisation measures:* Where appropriate, information should be provided in the Protocol and the IB on the measures that should be put in place to protect clinical trial subjects from identified risks. For example, if the results of the sterility test of the product are not available at release, appropriate mitigation measures should be described, including liaison with clinical staff where out of specification test results (for sterility) are obtained after the release of the product.

- *Upstream interventions on subjects:* In an autologous setting, the patient undergoes a medical intervention to extract cells/tissues prior to the manufacture and administration of the investigational medicinal product. The process of taking biopsies/extracting cells may entail risks to the subject and may also have an impact on the quality and safety of the product. Therefore, when such processes deviate from standard clinical practice (e.g. the collection of cells is done through leukapheresis but the conduct of the leukapheresis requires specific adaptation), they should be clearly explained. The level of documentation should be adapted to the complexity and the novelty of the procedure. It is acceptable that detailed instructions are laid down in a separate document available

at the site, provided that this document is also submitted as part of the application (e.g. attached as Annex to the Protocol or IB.)

- *Administration procedures:* When the administration process deviates from standard clinical practice, the detailed instructions for administration should be described in the Protocol or IB. It is acceptable that detailed instructions are laid down in a separate document available at the site, provided this document is also submitted as part of the application (e.g. attached as Annex to the Protocol or IB.) The level of documentation should take into account the complexity and novelty of the procedure. Where appropriate (i.e. in the case of complex administration procedure), training should be provided to those involved in the process. The presence of the sponsor (or a representative thereof) during the administration of the ATP to the clinical trial subject or in any upstream collection procedure is only acceptable if it is duly justified. If such presence is envisaged before the start of the clinical trial, this should be explained in the informed consent.

- *Traceability:* The use of each investigational medicinal product should be traceable. The individual product should be traceable from delivery to the clinical trial site up to the administration to the clinical trial subject. When the investigational product is an ATP that contains cells or tissues of human origin, the traceability from the recipient of the product to the donor of the cells or tissues should be ensured. The traceability system should be bidirectional (from donor to subject and from subject to donor) and data should be kept for 30 years after the expiry date of the product, unless a longer time period is required in the clinical trial authorization. For cells and tissues used as starting materials for ATPs, they should be traceable from the point of donation.

  The sponsor should ensure that the manufacturer of the investigational ATP has set up a system that enables the bidirectional tracking of cells/tissues contained in ATPs. The sponsor should also provide the investigator with detailed instructions to ensure traceability of the cells/tissues contained in the investigational ATP. The role and responsibilities of the manufacturer, the sponsor and the investigator in the implementation of the traceability system should be clearly documented, as well as the location of the traceability records. Traceability data should be kept also in cases where the clinical trial is suspended or prematurely ended.

- *Retention of samples:* Under general GCP principles, the sponsor should maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm

specifications. However, it is acknowledged that the retention of samples of the investigational ATPs containing or consisting of cells and tissues may be challenging due to the scarcity of the materials. Due to this intrinsic limitation, photographs clearly presenting the required information of each batch of finished products should be retained for a period of not less than 1 year after the expiry date of the products.

- *Informed consent:* Subjects that participate in clinical trials with ATPs should receive comprehensive information on the expected benefits and risks of the product, including the risk of treatment failure and effects of the treatment on the future use of other therapies for the diagnosis or treatment of the disease, as well as risks associated with upstream interventions or the administration procedure.

  Where applicable, the subject should also be informed of the irreversible nature of the ATP, and of risks to close contacts and off-springs, or if the treatment could compromise future pregnancies.

  The need for long-term follow-up and/or arrangements for remote follow-up should be clearly communicated, where applicable, and subject commitment should be sought (also in respect of any eventual collection of samples).

  The subject should be informed when the sponsor (or a representative thereof) is present during the upstream collection of cells/tissues and/or administration procedure.

- *Long-term follow-up:* The safety profile for some investigational ATPs may not be fully elucidated, in particular with respect to long-term effects. The duration of the biological activity of a given ATP should be taken into consideration when determining the need of subject follow-up. Where applicable, the establishment of a scheme for long-term follow-up should be described in the Protocol (or an associated document) and it should be clearly specified -where appropriate- which follow-up activities take place after the end of the clinical trial (e.g. interventional clinical trial or non-interventional follow-up). As such, the definition of "end of the trial" should be clear and unambiguous.

  The length of the observation period should be based on a risk-assessment having regard to all information available to the sponsor, including –as appropriate- factors such as the observed duration of vector persistence, ability to integrate, potential for latent

persistence and reactivation, duration of transgene expression, as well as non-clinical data and/or experience with relevant products. In assessing whether bibliographic data from other products is relevant, account has to be taken not only of the similarity of the product, including the transgene expressed and the administration route. If the risk of delayed adverse events is low, long-term follow-up is not required.

Detailed arrangements for the remote conduct of follow-up activities should be explained in the Protocol or an associated document. The sponsor is responsible to ensure that a robust system for the collection of adverse events is in place and he/she should explain in the Protocol (or associated document) how the quality of the data collected will be ensured. All data collected should be centralised and be available for inspection at the clinical trial site.

When long-term follow-up is foreseen in the Protocol, monitoring of subjects treated should also be ensured in cases of early termination of the clinical trials. The sponsor should also ensure that there is a process in place for follow-up of the subjects treated with the product in cases where the product development is discontinued or the (former) sponsor ceases to exist, for instance, by providing appropriate information to the healthcare establishments involved in the clinical trial. If the product development is transferred to another entity, responsibility for the follow-up obligations of treated patients should be transferred to the new owner.

Depending on the characteristics of the ATP, patient alert cards may need to be provided to subjects participating in ATP trials, with the objective of informing treating physicians about the product used with a view to facilitate medical care of the patient in case of an emergency and to facilitate reporting of adverse events. Alert cards should contain -as a minimum- the name of the subject, an investigator contact number and information regarding the medical treatment received.

- *Administration of out of specification products:* When defining the release specifications, the variability in the nature of the ATPs should be taken into consideration. Exceptionally, in cases where the release specifications as set out in the investigational medicinal product dossier are not met but the administration of the cells/tissues that are contained in a cell/tissue based ATP is necessary to avoid an immediate significant hazard to the subject, taking into account the alternative options for the subject and the consequences

of not receiving the cells/tissues contained in the product, the supply of the product to the investigator is justified. Under this circumstances, the handling procedure and documentation required for such use should be specified. (e.g. When the request of the investigator is received, the manufacturer/sponsor should provide him/her with its evaluation of the risks. Records of the investigator's request should be kept in the manufacturing site. The particular patient should then be informed accordingly.)

- *Safety reporting:* The sponsor should provide information and, as appropriate, training to the investigator on any additional Protocol and/or product specific requirements for the reporting of adverse events. For further details on ADRs reporting, please refer to the ***Guidance for Pharmaceutical Industry – Adverse Drug Reaction Reporting Requirements*** (http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/adr_reporting/index.html).

- *Monitoring:* The sponsor should adequately monitor the conduct of the clinical trial in accordance with the ICH guidelines on good clinical practice. In the case of ATPs that contain cells or tissues of human origin, monitoring activities should also cover compliance with the traceability requirements. Where applicable, compliance with the arrangements for long-term follow-up to subjects (as described in the Protocol) should also be verified.

Reference

1. European Commission. (2019). Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products
https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/atmp_guidelines_en.pdf

2. European Medicines Agency. (2019). Guideline on Quality, Non-clinical and Clinical Requirements for Investigational Advanced Therapy Medicinal Products in Clinical Trials (EMA/CAT/852602/2018 under consultation)
https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-clinical-requirements-investigational-advanced-therapy_en.pdf

Appendix 5 CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first. last)	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE Years	3. SEX	4-6 REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab date)										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING ☐ CONGENITAL ANOMALY

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20. DID REACTION ABATE AFTER STOPPING DRUGS? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRO-DUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period. etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER		
	24b. MFR CONTROL NO.	
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL	
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP	

Appendix 6 Clinical Trial Yearly Progress Report for ATP

Report period _____ to _____ Date of this report_____

CT cert no.:	
Protocol no.:	
Protocol title:	

Start date: _____ Anticipated end of trial date: _____

Target no. of patient (as stated in protocol) _____
No. of patient intend to recruit (per centre) _____
No. of patient recruited (per centre) _____
No. of patient completed the trial (per centre) _____
No. of patient drop-out from study (per centre) _____
Reasons for drop-out:

Any changes for principal investigator? (If yes please give details)

Summary of amendments during report period (if any)

Summary of Serious Adverse Events (if any)

Does SAE affect the study?
How and what action has been taken?

Summary of complaints about the study (if any)

Summary of recent findings (especially information about risks associated with the research)

Progress of study:

☐ According to plan
☐ Extend study period (reason_____)
☐ Premature termination (reason_____)

Name:_____ Signature:_____
Posting: _____ Date:_____

Appendix 7 Clinical Trial Final Report for ATP

Report period _____ to _____ Date of this report_____

CT cert no.:	
Protocol no.:	
Protocol title:	

Start date: _____ End of trial date: _____

Target no. of patient (as stated in protocol) _____
No. of patient intend to recruit (per centre) _____
No. of patient recruited (per centre) _____
No. of patient completed the trial (per centre) _____
No. of patient drop-out from study (per centre) _____
Reasons for drop-out:

Summary of Serious Adverse Events (if any)

Does SAE affect the study?
How and what action has been taken?

Summary of complaints about the study (if any)

Study duration:
☐ According to plan
☐ Extend study period (reason_____)
☐ Premature termination (reason_____)

Summary of study outcome

Name:_____ Signature:_____
Posting:_____ Date:_____

Appendix 8 Statement of Purposes

Purpose of collection

1. The personal data provided by certificate applicants are for the purposes of application for certificate under the Pharmacy and Poisons Ordinance. The personal data provided will be used by the Department of Health for the following purposes:

(a) Proof of eligibility for a certificate

(b) Assessment of whether the applicant is a fit and proper person to be granted a certificate

2. The provision of personal data is voluntary. If you do not provide sufficient information, we may not be able to prove your eligibility for a certificate, or to assess whether you are a fit and proper person to be granted a certificate.

Classes of Transferees

3. The personal data you provide are mainly for use within the Department of Health and the Pharmacy and Poisons Board. Apart from this, the data may only be disclosed to parties where you have given consent to such disclosure or where such disclosure is allowed under the Personal Data (Privacy) Ordinance.

Access to Personal Data

4. You have a right of access and correction with respect to the personal data as provided in sections 18 and 22 and Principle 6 of Schedule 1 of the Personal Data (Privacy) Ordinance. Your right of access includes the right to obtain a copy of your personal data. A fee may be imposed for complying with a data access request.

Enquiries

5. Enquiries concerning the provided personal data, including the making of access and corrections, should be addressed to:

Senior Pharmacist
Drug Evaluation and Import/Export Control Division
Drug Office, Department of Health
Suites 2002-05, 20/F, AIA Kowloon Tower
Landmark East, 100 How Ming Street
Kwun Tong, Kowloon
Tel: 3974 4175

Document Information

Version	Date	Description of Change
1.0	29.10.2019	First version (Draft for comment)
1.0.1	13.01.2020	First version (Draft for comment) • Update of contact information