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

Version 3.1

Pharmacy and Poisons Board of Hong Kong

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 Relevant definitions of gene therapy product, somatic cell therapy product and tissue engineered product are set out in section 2 of the PPO.

1.5 To be in line with international practice, the ATP definition covers the products intended for use in human but not animal. Of note, blood transfusion, cornea transplant and bone marrow transplant are not considered as ATPs. Applicant should refer to 'Guidance on

Classification of Advanced Therapy Products'[1] to determine whether the product under application falls within the ATP definition.

1.6 According to Regulation 36(1) of the Pharmacy and Poisons Regulations, Cap. 138A (PPR), no person shall sell, offer for sale or distribute or possess for the purposes of sale, distribution or other use any pharmaceutical product or substance unless the product or substance is registered with the Pharmacy and Poisons Board (the "Board").

1.7 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 of Drug/Product Registration. The Drug Office of Department of Health (DH DO) is the executive arm of the Committee.

1.8 Your ATP will only be approved for registration if it meets the criteria of safety, efficacy and quality relevant to it.

[1] 'Guidance on Classification of Advanced Therapy Products' is available at: https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

2. Purpose of this Guidance

2.1 This guidance outlines the procedures and requirements for the application of the Certificate of Drug/Product Registration (the "Registration Certificate") for ATP.

2.2 The technical requirements for The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Common Technical Document (CTD) Modules 3 to 5 for pharmaceutical products apply to registration of ATP. This guidance also describes the specific requirements for these modules for registration of ATP.

3. Scope

3.1 This guidance applies to applicants for the Registration Certificate for ATP.

3.2 Applicant could be (one of the below):

- (if your ATP is manufactured in Hong Kong) the licensed manufacturer, or the licensed wholesale dealer contracting with the licensed manufacturer
- (if your ATP is manufactured outside Hong Kong) the licensed wholesale dealer who would import the product, or the Hong Kong branch, subsidiary, representative, agent or distributor of the overseas manufacturer

4. How to apply

You should submit your new application via 'Pharmaceutical Registration System 2.0' (PRS2.0) (https://www.drugoffice.gov.hk/prs2-ext/client_authentication.jsp) with particulars listed in paragraph 4.2.

4.1 The application fee, currently at $1,100, to be paid via PRS 2.0 with credit card/PPS online payment services, or in person by cash or cheque along with the notification of payment at the following address:

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)

(Office hours:
Monday to Friday
9 am to 1 pm and 2 pm to 5:45pm
(up to 6 pm on Monday)
Shroff closes 15 minutes earlier
Closed on Saturdays, Sundays and Public Holidays)

4.2 Please submit the following particulars in your application:

(a) for ATPs manufactured outside Hong Kong, an authorization letter from the overseas manufacturer for the applicant is required;

(b) soft copy of the business registration certificate of the applicant;

(c) an authorized person for the application, contact telephone and facsimile numbers and content of the submission dossier. Please declare in the PRS 2.0 that the applicant "agrees to submit additional or updated supporting documents when required";

(d) soft copy and certified true copy* of the manufacturer's licence;

(e) for application relating to an ATP manufactured outside Hong Kong, the methods, standards and conditions of the manufacture of the ATP will also be taken into consideration. Applicants should therefore supply detailed information regarding the manufacturer including the manufacturing and quality control facilities, technical personnel, etc;

(f) soft copy and certified true copy* of Good Manufacturing Practice (GMP) certificate of the manufacturer(s). All applications for registration of ATPs must include evidence of manufacturers' compliance with the Pharmaceutical Inspection Co-operation Scheme (PIC/S) GMP standards;

(g) soft copy and original or certified true copy* of free sale certificate of the ATP issued by the country of origin;

(h) official evidence of registration approval of the product (e.g. soft copy and original or certified true copies* of free sale certificates) in :

two or more of the following countries[2]: Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Cyprus, Czech Republic, Denmark, Estonia, Finland,

* Soft copies of the above supporting documents must be submitted via the PRS2.0 in PDF format. Their original or certified true copies should be submitted to the address shown in paragraph 4.1 above.

[2] Approvals from the EU countries must be issued from European Medicines Agency; for an advanced therapy product that meets the criteria set out in paragraph 4.1.2 of the "Guidance Notes on Registration of Pharmaceutical Products Containing a New Chemical or Biological Entity" while being supported with additional

France, Germany, Greece, Holland, Hungary, Ireland, Italy, Japan, Republic of Korea, Latvia, Lithuania, Luxembourg, Malta, Poland, Portugal, Romania, Singapore, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, UK and USA;

(i) one set of prototype sales pack (e.g. infusion bag label, and other component(s) comprising the sales pack) for each pack size of the ATP, complying with the labelling requirements as specified in 'Guidelines on the Labelling of Pharmaceutical Products'[3] and 'Guidance on Labelling Requirements of Product Code, Unique Donation Identifier and Unique Recipient Identifier for Advanced Therapy Products'[4]. For ATP, the label should contain product code and unique donation identifier. For autologous product, unique recipient identifier is also required. The coding systems adopted should be specified;

(j) JPEG format (pixel size not less than 320x200) of your prototype sales pack or sample sales pack, including the inner container/packaging and the unit dose form image of the product sample, clearly showing the complete content of the prototype sales pack and its component(s), for example:

- colour of the dose form (e.g. solution for infusion, suspension for infusion);
- appearance of the container (e.g infusion bag, vial);

(k) proposed package insert of the product. A prescribing information leaflet for healthcare professionals for use in Hong Kong is required;

(l) documentary evidence showing that the package insert has been approved by one of the listed countries in paragraph 4.2(h) above to support the proposed indication(s), dosage, route of administration and other contents of the package insert (if any) (Cross-referencing to documents should be made by referring to the

documentary evidence as stated in the ensuing paragraphs therein, its application for registration may be accepted for evaluation on a case-by-case basis and processed within a defined timeframe, subject to other requirements set out in this set of Guidance Notes.

[3] 'Guidelines on the Labelling of Pharmaceutical Products' is available at: https://www.ppbhk.org.hk/eng/doc/guidelines_forms/Label_Gl_en.pdf

[4] 'Guidance on Labelling Requirements of Product Code, Unique Donation Identifier and Unique Recipient Identifier for Advanced Therapy Products' is available at: https://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/atp_regulation.html

page number of the reference documents and the relevant parts of the reference documents should be highlighted clearly);

(m) relevant Risk Management Plan (RMP) approved by reputable regulatory authority(ies) is/ are required for the product. Information on whether any of the RMP activities and mitigation strategies will be implemented in Hong Kong;

(n) for materials of animal origin used in the manufacturing of the product, documentary evidence should be provided to show compliance with one or more of the safety measures taken to minimize the risk of communicable diseases that can be transmitted to human, including but not limited to Transmissible Spongiform Encephalopathy (TSE) transmission;

(o) for materials of human origin (e.g. albumin) used in the manufacturing of the product, documentary evidence (e.g. certificate of approval of plasma issued by regulatory authority) should be provided to show that the risk associated with the materials used is considered negligible and the product can be classified as safe according to current scientific knowledge and does not impose an additional risk to patients;

(p) curriculum vitae and signature of the experts who are responsible for writing the quality overall summary, non-clinical and clinical overviews, respectively;

(q) ICH CTD Modules 2 to 5[5&6] including (but not limited to):

i) information on all starting materials (including vector, cell and tissue, etc.) used to manufacture of the active substances;

ii) manufacturing processes and quality control of the active substance(s) and the finished product;

iii) detailed and complete qualitative and quantitative composition of the finished product issued by the manufacturer;

[5] Please refer to Appendices 1-3 for the specific requirements for the CTD Modules 3 to 5 respectively for each type of ATPs.

[6] Applicant should declare that the CTD Modules submitted to DH DO are those approved by one of the listed countries in paragraph 4.2(h) above. Please highlight the discrepancy (if any) and provide justification accordingly.

iv) specifications of the product issued by the manufacturer;

v) detailed method of analysis of the product for all tests stated in the finished product specifications;

vi) certificate of analysis of a representative batch of the finished product issued by the manufacturer or the company performing the analysis;

vii) stability test data to support the shelf-life and storage conditions of the product; and

viii) a description of the traceability system.

For additional reference materials on ATP registration, applicants may also refer to relevant guidelines for gene, cellular and tissue based therapies issued by reputable reference agencies such as European Medicines Agency and the United States Food and Drug Administration.

5. Registration fee

5.1 When an application is approved, you will be required to pay a registration fee of $1,370 per product. You will receive the Registration Certificate when we have received the payment. Please pay by post, or via the PRS2.0 with credit card/PPS online payment services, or in person at the address specified in paragraph 4.1 above. Cheques should be made payable to "The Government of the Hong Kong Special Administrative Region" and crossed.

6. Infringement of patent right

6.1 Please note that the Board does not take into consideration of the factor of patent right while deciding on an application of the Registration Certificate for ATP. Nevertheless, an applicant shall not overlook the issue of infringement of patent right as doing the following acts in Hong Kong without the consent of the patent proprietor may be liable for infringement of a patent registered in Hong Kong:

- making, putting on the market, using or importing a patented product
- stocking the patented product whether for the purpose of putting it on the market (in Hong Kong or elsewhere) or otherwise

6.2 You are therefore reminded to ensure that your product does not infringe any patent right. Please see sections 73 to 75 of the Patents Ordinance (Cap. 514) for further details. You should always consult your lawyer if you have any doubts on this issue.

7. "Regulated Product" under Human Organ Transplant Ordinance

7.1 A product which falls within the definition of "organ" and has been subjected to "processing" as stipulated in the Human Organ Transplant Ordinance, Cap. 465 (HOTO) may be regarded as a "Regulated Product"[7&8]. If the ATP to be registered falls into the definition of "regulated product" in the HOTO, an application for exemption[9] of Regulated Product under the HOTO is required. Applicant may submit relevant dossier to DH DO.

7.2 Director of Health may, on application[10], exempt a Regulated Product from the application of the whole or any part(s) of the HOTO if:

- the product for transplant purpose is safe and has no adverse impact on public health
- the donor of the tissues concerned has given his consent to the removal of the tissues for the purpose of producing the product without coercion or the offer of inducement
- no payment has been made or is intended to be made to that donor

[7] According to section 7A(1) of the Human Organ Transplant Ordinance (Cap. 465), a "regulated product" means a product containing any structured arrangement of tissues that- a. falls within paragraph (a)(iii) of the definition of "organ" in section 2 of the Ordinance: "Organ" means any structured arrangement of tissues forming part of any human bodily part which consists of a structured arrangement of tissues; and if wholly removed, cannot be regenerated by the body; or any structured arrangement of tissues forming part of any human bodily part specified in the Schedule of the Ordinance, that is blood (including cord blood) and bone marrow; and b. has been subjected to processing: "Processing", in relation to any structured arrangement of tissues, means any activity performed on the tissues that 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.

[8] Skin and bone derived products are some examples of regulated products. The scope of regulated products does not cover autologous therapeutic products. Please refer to: https://www.dh.gov.hk/english/useful/useful_hot_exemption/useful_FrequentlyAskedExemption.html

[9] If the ATP under application for registration is also a "regulated product" as defined in the Human Organ Transplant Ordinance (Cap. 465), it is also subject to all statutory requirements under the Ordinance unless an exemption has been granted by the Director of Health. Please refer to the Part 7 of Cap. 465 for further details at: https://www.elegislation.gov.hk/hk/cap465

[10] For detail of application for exemption of regulated product, please refer to the website: https://www.dh.gov.hk/english/useful/useful_hot_exemption/useful_hta.html

8. Enquiries on progress of applications

8.1 At any time during the application, you can make enquiry at the Drug Registration Unit, DH DO regarding the progress of the application. Please quote the file reference of the registration application when making enquiry.

8.2 This document serves as a general guide to the applicant for the Registration Certificate for ATP and shall not be regarded as the complete registration requirements or authoritative statement of the relevant laws or the interpretation on any particular case. Copies of the Pharmacy and Poisons Ordinance and its subsidiary legislations shall be referred, which can be purchased by calling the Publications Sales Section, Information Services Department at 25371910, or by email at: puborder@isd.gov.hk. Contents of the relevant legislation can also be found at the website of Department of Justice at: https://www.elegislation.gov.hk

9. Remarks

9.1 After the product registration is approved, the Registration Certificate holder is responsible for ensuring the registrable particulars of the product that correspond exactly with those approved by the Board. The Registration Certificate holder should refer to 'Guidance Notes on Change of Registered Particulars of Registered Pharmaceutical Products/Substances'[11] for any change of registered particulars as stipulated in regulation 36A(2) of the PPR after product registration.

[11] 'Guidance Notes on Change of Registered Particulars of Registered Pharmaceutical Products/Substances' is available at: https://www.ppbhk.org.hk/eng/doc/guidelines_forms/copGuide_en.pdf

9.2 The Registration Certificate is valid for 5 years, and it shall be renewable on payment of prescribed fee and provision of up-to-date information specified by the Committee as stipulated in regulation 36(7) of the PPR. For details, please refer to the website: http://www.drugoffice.gov.hk/eps/do/en/pharmaceutical_trade/guidelines_forms/renewal_product_pp.html

Appendix 1 Specific Requirements for Module 3

A1.1 For all ATPs

- A description of the traceability system that the Registration Certificate holder intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private healthcare facilities where the product is used, should be provided.

A1.2 For gene therapy product

- Information should be provided on all starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells, taking into consideration the possible absence of purification steps.
- For products containing a virus or a microorganism, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the virus or microorganism, pathogenicity and characteristics of the parental strain should be provided.
- The process-related impurities and product-related impurities should be described in the relevant sections of the dossier, and in particularly replication competent virus contaminants if the vector is designed to be replication incompetent.
- For plasmids, quantification of the different plasmid forms should be undertaken throughout the shelf life of the product.
- For genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, should be tested.

- For genetically modified cells, in addition to the specific requirements for gene therapy products, the quality requirements for somatic cell therapy products and tissue engineered products under paragraph A1.3 should apply.

A1.3 For somatic cell therapy products and tissue engineered products

A1.3.1 Starting materials

(a) Summary information on donation, procurement and testing of the human tissue and cells used as starting materials should be provided. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use should be justified.

(b) The pooling strategies and measures to ensure traceability should be described if allogeneic cell populations are being pooled.

(c) The potential variability introduced through the human or animal tissues and cells should be addressed as part of the validation of the manufacturing process, characterisation of the active substance and the finished product, development of assays, setting of specifications and stability.

(d) For xenogeneic cell-based products, information on the animal source (e.g. geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities should be provided.

(e) For cell-based products derived from genetically modified animals, detailed description of the specific characteristics of the cells related to the genetic modification, the method of creation and the characterisation of the transgenic animal should be provided.

(f) The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with

"engineered cells"[12] of which they form an integral part, should be described and justified.

(g) For the devices contained into the ATPs, the information required under section A1.4 for the evaluation of the product should be provided.

(h) In the case of genetic modification of cells, the technical requirements specified for gene therapy product under section A1.2 should apply.

A1.3.2 Manufacturing process

(a) The manufacturing process should be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.

(b) If cells are grown directly inside or on a matrix, scaffold or device, information on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination should be provided.

A1.3.3 Characterisation and control strategy

(a) Relevant information on the characterisation of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants), viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use should be provided. The genetic stability of the cells should be demonstrated.

(b) Qualitative and, where possible, quantitative information on product-related impurities, process-related impurities, and any material capable of introducing degradation products during production, should be provided. The extent of the determination of impurities should be justified.

[12] "Engineered cells" as defined in 'DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use'.

(c) Justification should be provided if certain release tests can only be performed on key intermediates and/or as in-process testing but not on the active substance or finished product.

(d) Where biologically active molecules (e.g. growth factors or cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance should be characterised.

(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organisation of the cells and, where applicable, the extracellular matrix generated should be part of the characterisation for these cell-based products. Where needed, non-clinical investigations should complement the physicochemical characterization.

A1.3.4 Excipients: For excipient(s) used in cell or tissue-based products (e.g. the components of the transport medium), the requirements for novel excipients should apply unless data exists on the interactions between the cells or tissues and the excipients.

A1.3.5 Developmental studies: The description of the development program should address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation should be discussed.

A1.3.6 Reference materials: A reference standard, relevant and specific for the active substance and/or the finished product, should be documented and characterised.

A1.4 For ATPs containing devices

- A description of the physical characteristics and performance of the product and a description of the product design methods should be provided.
- The interaction and compatibility between the device and the other components of the product including genes, cells and/or tissues should be provided.

Reference

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Appendix 2 Specific Requirements for Module 4

A2.1 For all ATPs

- The rationale for the non-clinical development and the criteria used to choose the relevant species and models (*in vitro* and *in vivo*) should be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanised or transgenic animals. The use of homologous models (e.g. mouse cells analysed in mice) or disease mimicking models should be considered, especially for immunogenicity and immunotoxicity studies.
- The safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, should be provided. Their physical, mechanical, chemical and biological properties should be considered.

A2.2 For gene therapy product

A2.2.1 In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy product should be taken into account.

A2.2.2 <u>Pharmacology</u>

(a) *In vitro* and *in vivo* studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamics 'proof of concept' studies) should be provided using models and relevant animal species designed to demonstrate the nucleic acid sequence reaching its intended target (target organ or cells) and providing its intended function (level of expression and functional activity). The duration of

the nucleic acid sequence function and the proposed dosing regimen in the clinical studies should be provided.

(b) Target selectivity: For the gene therapy product intended to have a selective or target-restricted functionality, studies should be provided to confirm the specificity and duration of functionality and activity in target cells and tissues.

A2.2.3 Pharmacokinetics

(a) Biodistribution studies should include investigations on persistence, clearance and mobilisation. Biodistribution studies should additionally address the risk of germline transmission.

(b) Investigations of shedding and risk of transmission to third parties should be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

A2.2.4 Toxicology

(a) Toxicity of the finished gene therapy product should be assessed. Depending on the type of product, individual testing of active substance and excipients should be considered, and the *in vivo* effect of expressed nucleic acid sequence-related products which are not intended for the physiological function should be evaluated.

(b) Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

(c) When multiple dosing of human subjects is intended, repeated dose toxicity studies should be provided. The mode and scheme of administration should closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies should be considered. Depending on the persistence

of the gene therapy product and the anticipated potential risks, the duration of the studies may be longer than in standard toxicity studies. A justification for the duration should be provided.

(d) Genotoxicity should be studied. However, standard genotoxicity studies should only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

(e) Carcinogenicity should be studied. Standard lifetime rodent carcinogenicity studies would not be required. However, depending on the type of product, the tumourigenic potential should be evaluated in relevant *in vivo/in vitro* models.

(f) Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function should be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies should be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

(g) Additional toxicity studies: Integration studies should be provided for any gene therapy product unless the lack of these studies is scientifically justified (e.g. because nucleic acid sequences will not enter into the cell nucleus). For the gene therapy product which is not expected to be capable of integration, integration studies should be performed, if biodistribution data indicates a risk for germline transmission. Studies on the potential immunogenic and immunotoxic effects should also be included in the dossier.

A2.3 For somatic cell therapy products and tissue engineered products

A2.3.1 Pharmacology

(a) The primary pharmacological studies should be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue should be studied.

(b) The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing should be determined.

(c) Secondary pharmacological studies should be considered to evaluate potential physiological effects that are not related to the desired therapeutic effect of the product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

A2.3.2 Pharmacokinetics

(a) Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion would not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration should be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

(b) Distribution, duration and amount of expression of the systemically active biomolecules produced by the product should be studied.

A2.3.3 Toxicology

(a) The toxicity of the finished product should be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities should be considered.

(b) The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the product, together with its pharmacodynamic and pharmacokinetic profile, should be taken into consideration. A justification of the duration should be provided.

(c) Conventional carcinogenicity and genotoxicity studies would not be required, except with regard to the tumourigenic potential of the product.

(d) Potential immunogenic and immunotoxic effects should be studied.

(e) For cell-based products containing or consisting of animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens should be addressed.

Reference

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Appendix 3 Specific Requirements for Module 5

A3.1 For all ATPs

- Where the clinical application of ATPs requires specific concomitant therapy and involves surgical procedures, the therapeutic procedure as a whole should be investigated and described. Information on the standardisation and optimisation of those procedures during clinical development should be provided.
- Where devices used during the surgical procedures for application, implantation or administration of the ATP may have an impact on the efficacy or safety of the ATP, information on these devices should be provided.
- Specific expertise required to carry out the application, implantation, administration or follow-up activities should be defined. The training plan of health care professionals on the use, application, implantation or administration procedures of these products should be provided where necessary.
- Given that, due to the nature of ATPs, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.
- During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk should be addressed.
- Dose selection and schedule of use should be defined by dose-finding studies.
- The efficacy of the proposed indications should be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. Evidence of long-term efficacy may be required in certain clinical conditions. The strategy to evaluate long-term efficacy should be provided.
- A strategy for the long-term follow-up of safety and efficacy should be included in the RMP.
- For ATPs containing devices, the safety and efficacy studies should be designed for and performed on the product as a whole.

A3.2 For gene therapy product

- Human pharmacokinetic studies should include the following aspects: shedding studies to address the excretion of the gene therapy products; biodistribution studies; and pharmacokinetic studies of the product and the gene expression moieties (e.g. expressed proteins or genomic signatures).
- Human pharmacodynamic studies should address the expression and function of the nucleic acid sequence following administration of the gene therapy product.
- Safety studies should address the following aspects: emergence of replication competent vector; emergence of new strains; reassortment of existing genomic sequences; and neoplastic proliferation due to insertional mutagenicity.

A3.3 For somatic cell therapy products

- The biodistribution, persistence and long-term engraftment of the somatic cell therapy product components should be addressed during the clinical development.
- Safety studies should address the following aspects: distribution and engrafting following administration; ectopic engraftment; and oncogenic transformation and cell/tissue lineage fidelity.
- For somatic cell therapy products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules should be addressed, if feasible.

A3.4 For tissue engineered products

- Where conventional pharmacokinetic studies are not relevant for the product, the biodistribution, persistence and degradation of the product components should be addressed during the clinical development.
- Pharmacodynamic studies should be designed and tailored to the specificities of the product. The evidence for the 'proof of concept' and the kinetics of the product to obtain

the intended regeneration, repairing or replacement should be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure should be taken into consideration.

- Safety studies should address the following aspects: distribution and engrafting following administration; ectopic engraftment; and oncogenic transformation and cell/tissue lineage fidelity.

Reference

DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use. https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

Document Information

Version	Date	Description of Change
1.0	1 August 2021	(First version issued in June 2021)
2.0	1 November 2022	Update of the list of reference countries
3.0	23 February 2023	Update of registration requirements
3.1	1 November 2024	Cross-referencing to paragraph 4 "Special Considerations" under the Guidance Notes on Registration of Pharmaceutical Products Containing a New Chemical or Biological Entity

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