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Regulatory guide for ATMPs: a generic process guide from the pre-clinical to clinical development phase for ATMPs

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This document contains compiled information from:

The Cell Therapy Guide (Karolinska Trial Alliance and GE Healthcare), European Medicines Agency, International Council for Harmonisation, Inspektionen för vård och omsorg, Kliniska studier i Sverige, Läkemedelsverket, Socialstyrelsen, US Food and Drug Administration, Vävnadsrådet.

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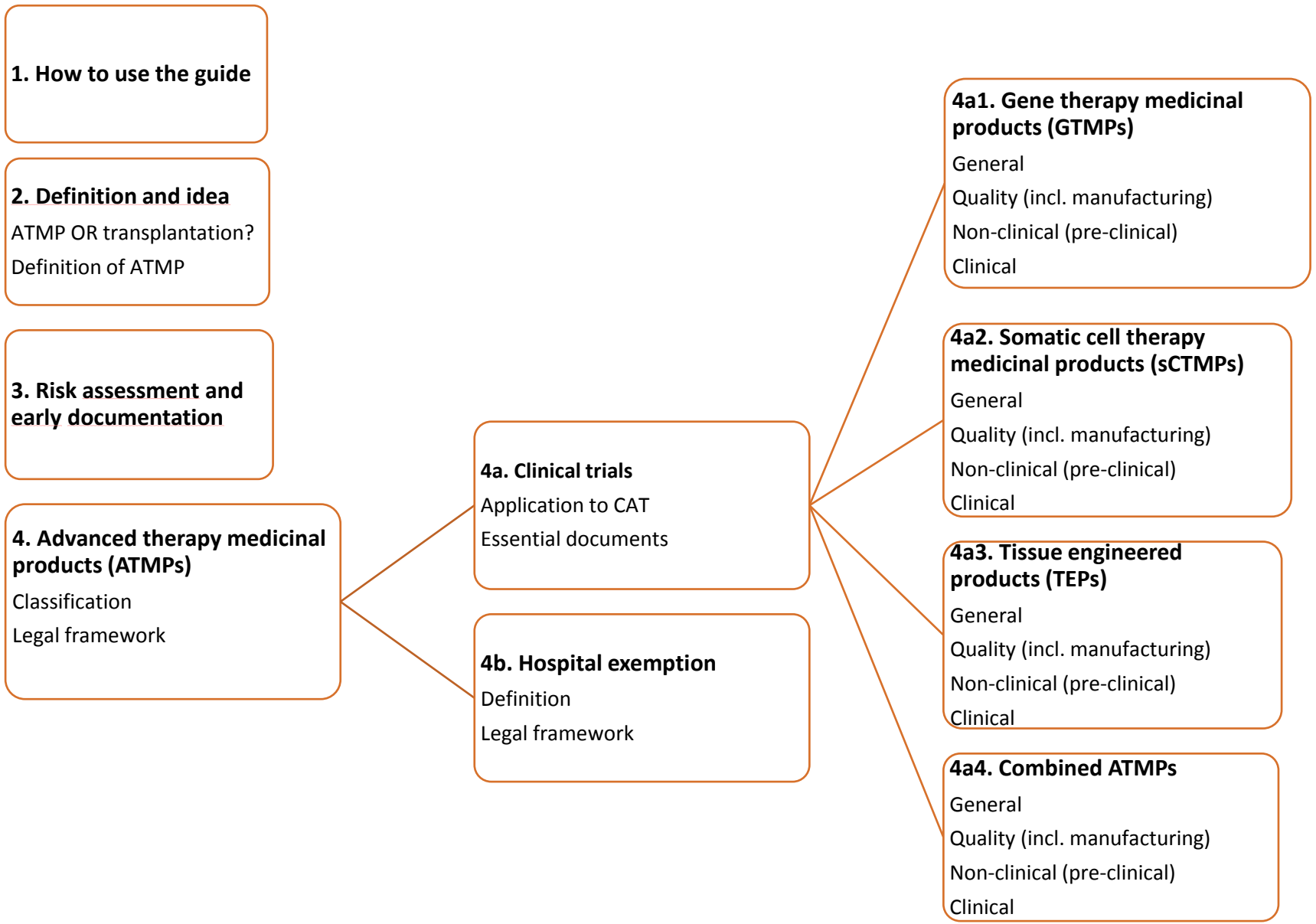
Abbreviations:

ATMP	Advanced therapy medicinal product
CAT	Committee for Advanced Therapies
EMA	European Medicines Agency
GCP	Good clinical practice
GDP	Good distribution practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GTMP	Gene therapy medicinal product
IB	Investigators brochure
IMP	Investigational medicinal product
IMPD	Investigational medicinal product dossier
sCTMP	Somatic cell therapy medicinal product
TEP	Tissue engineered product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1. How to use this guide

This regulatory guide will provide useful information and insights throughout the Advanced Therapy Medicinal Product (ATMP) development process. In general:

- It is important to document all steps from the start and throughout the whole process from the initial idea to an ATMP.
- Contact Läkemedelsverket or the European Medicines Agency (EMA) at an early stage for advice on your process development plan.

This guide for ATMPs will help you through the important steps from process development to clinical use. But remember, you are the one who knows your product best. Some of the most essential topics to consider are:

- identifying your starting material
- raw materials specifications
- risk assessment
- early documentation
- production process
- product specification
- quality controls
- contract manufacturing or in-house manufacture process.
- Will there be a need of transport of product?

Throughout the process guide, the following topics are presented for each class of ATMP:

- **General:** information
- **Quality (including manufacturing):** characterisation, consistency, potency and comparability
- **Non-clinical (pre-clinical):** adequate animal models, mechanism of action, bio-distribution and safety
- **Clinical:** safety, long-term efficacy, general endpoints + specific endpoint and duration of follow-up

2. Definition of product and idea

Definition of product

ATMPs are medicinal products that are based on tissues, cells or genes. A distinction is made between ATMPs and tissues/cells for transplantation depending on how the tissue/cells are processed and/or used clinically. The definition of an ATMP is a product that has been substantially manipulated or a product not intended for the same essential function in the recipient and the donor, for more information, please read Regulation 1394/2007/EC and Reflection paper on the classification of advanced therapy medicinal products (see below for non-homologous use). A typical example where a product is used for another function is when bone-marrow derived stem cells are injected in the myocardium intended for post-myocardial infarction cardiac repair. Products for treating patients with cells that have been subjected to non-substantial manipulation are not considered as ATMPs. If it is unclear whether a product is an ATMP or not, contact Läkemedelsverket and Inspektionen för vård och omsorg.

The list below (Ref: Annex 1 of Regulation (EC) No 1394/2007) describes non-substantial manipulations that, in particular, should not be considered as substantial manipulations:

- Cutting
- Grinding
- Shaping
- Centrifugation
- Soaking in antibiotic or antimicrobial solutions
- Sterilisation
- Irradiation
- Cell separation, concentration or purification
- Filtering
- Lyophilisation
- Freezing
- Cryopreservation
- Vitrification

Further reading for tissue/cell transplantation (not ATMP):

- Inspektionen för vård och omsorg: tissue establishment authorisation (tissue/cell transplantation not ATMP): Tissue establishment authorisation| IVO.se (in Swedish)
- Socialstyrelsen: Regulation of tissue establishment:
  - Donating and procuring tissue and cells: SOSFS 2009:30 (in Swedish)
  - Tissue establishment in healthcare: SOSFS 2009:31 (in Swedish)
  - Using tissue and cells in healthcare for clinical research: SOSFS 2009:32 (in Swedish)

Product idea

The product idea includes:

- Identifying the starting material (i.e. tissues/cells, autologous/allogenic)
- Defining the product: mode of administration and mechanism of action
- Defining the production process.

3. Risk assessment and early documentation

Due to the specific nature of ATMPs, a risk-based approach is necessary to determine the extent of quality, non-clinical and clinical data (including risk management plan and pharmacovigilance activities) to be performed.

Due to the risk aspect, early contact with Läkemedelsverket and EMA is important. A strategy to determine risk according to the marketing process is to follow the risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMP (PDF)

4. Advanced therapy medicinal products (ATMPs)

Classification

The EMA has a Committee for Advanced Therapies (CAT), which is responsible for assessing the quality, safety and efficacy of ATMPs and following scientific developments in the field. The committee is responsible for carrying out classifications of ATMPs. Classification is a non-mandatory, free of charge, legally non-binding procedure. The classification helps developers to clarify the applicable regulatory framework. It provides clarity on the development path and scientific-regulatory guidance to be followed. ATMP classification is based on the evaluation of whether a given product fulfils one of the definitions of a gene therapy medicinal product (GTMP), somatic cell therapy medicinal product (sCTMP) or tissue engineered product (TEP) and whether the product fulfils the definition of a combined ATMP or not. Classification focuses on the proposed mechanism of action of the ATMP.

The EMA publishes the assessment of ATMP classification as summary reports; EMA: definition of the classification. If the product to be used is not found in the summary reports, an application for classification can be submitted; apply for the classification. The CAT delivers scientific recommendations on ATMP classification after consultation with the European Commission within 60 days from receipt of the request.

The EMA has published the following guidance for help in classifying ATMPs:
Reflection paper on the classification of advanced therapy medicinal products
European Medicines Agency – advanced therapy classification – summaries of scientific recommendations for the classification of advanced therapy medicinal products

When preparing a submission for the classification of a combined ATMP (according to the EMA's advice):
1) The device part has a CE mark
- include administrative information regarding the medical device on the 'presubmission request form'. (p. 5)
- In the 'briefing document' (Word document), include sufficient information for the CAT to judge whether the device is integral with the cells/tissues (include this information in section 1.4 of the document). Also include in section 2.3, your rationale regarding how your product fulfils the definition of a combined ATMP.

2) The device part has no CE mark
- on the presubmission request form, complete the top part of page 5 which refers to 'medical device incorporated'
- in the briefing document, as above, include sufficient information for the CAT to judge whether the device is integral with the cells/tissues (include this information in section 1.4 of the document). Also include in section 2.3, your rationale regarding how your product fulfils the definition of a combined ATMP. Furthermore, clearly state that the structural component would fulfil the definition of a medical device (and justify your reasoning).

Legal framework

The regulatory framework for ATMPs is designed to give access to the EU market and guarantee health protection for patients. The regulatory aspects for ATMPs can be found on the EMA's web page: regulatory framework. Legislation on ATMP: (Regulation 1394/2007/EC) and Directive 2001/83/EC

Läkemedelsverket also provides guidance on ATMPs on its homepage:

- ATMP (in Swedish) – Läkemedelsverket
- Quality and safety regulations for human cell and tissue handling (in Swedish) – Läkemedelsverket

For procurement and manufacturing, permits are required from national authorities (Inspektionen för vård och omsorg and Läkemedelsverket):

- Donation and procurement of tissue and cells necessitates: SOSFS 2009:30 (in Swedish).
- For handling human tissues and cells to be used as raw material in the production of ATMPs, a tissue establishment authorisation (LVFS_2011-4 (in Swedish) and LVFS_2008-12 (in Swedish)) and manufacturing permit LVFS_2004-7 (in Swedish) are needed.
- A qualified person (QP) is needed; the necessary qualifications and responsibilities are described in LVFS 2004:7 and GMP vol. 4 Annex 16).
- Clinical trials for an ATMP require a permit from Läkemedelsverket (clinical approval (in Swedish) – Läkemedelsverket.
- For the protection of persons with regard to the processing of personal data, the General Data Protection Regulation GDPR directive must be followed.

GXP in relation to ATMPs

Non-clinical:

Generally, pivotal non-clinical safety studies should be performed under good laboratory practice (GLP). However, this may prove difficult due to the nature of ATMPs. It is recommended to seek advice from the relevant authority on the non-clinical safety programme before initiation, which also should include the GLP status of the intended studies or part of studies.

The principles of GLP that need to be taken into account in relation to ATMPs are described here: GLP in relation to ATMPs

Quality (including manufacturing)

The good manufacturing practice (GMP) guideline is a quality system that provides guidance for the production of pharmaceuticals (incl. manufacturing, testing and quality assurance). EudraLex (the rules governing medicinal products in the European Union) Volume 4 (EU guideline on good manufacturing practice for medicinal products for human and veterinary use) is useful for ATMPs:

The following guidelines are specific for ATMPs: GMP for ATMPs. Other documents developing GMP requirements for medicinal products which are contained in Volume 4 are not applicable to ATMPs, unless specific reference to them is made in these guidelines. The following documents are referenced and hence are applicable to ATMPs:

- Manufacture of biological active substances and medicinal products for human use: Annex 2
- Investigational medicinal products: Annex 13
- Certification by a qualified person and batch release: Annex 16

Documents relating to ATMPs

The following essential documents apply to quality.

- Setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells: Directive 2004/23/EC, Directive 2006/17/EC, Commission Directive (EU) 2015/566
- For all starting and raw materials derived from blood, the European blood directive and its technical directives should be considered: Directive 2002/98/EC
- Traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells: Directive 2006/86/EC, Commission Directive (EU) 2015/565
- Community code relating to medicinal products for human use regarding ATMPs: Directive 2009/120/EC
- Use of bovine serum in the manufacture of human biological medicinal products: Guideline CHMP/BWP/457920/2012 Rev. 1
- Good distribution practice (GDP) applies for medical products (Commission guideline 2013/C 343/01.

Clinical

Detailed guidelines on good clinical practice specific to ATMPs, GCP for ATMPs (EudraLex), and investigational medicinal products for human use, as well as the requirements for authorising the manufacture or import of such products: GCP Directive 2005/28/EC.

4a. Clinical trials

Classification of the ATMP under development must be established and the essential documents, such as the Investigational Medicinal Product Dossier (IMPD) and the Investigators brochure (IB), must be ready before submission of a clinical ATMP trial application.

Application to CAT

If the ATMP classification is not established, application to the CAT for classification is recommended. Classification is a non-mandatory, free-of-charge, non-legally binding procedure. Classification helps developers to clarify the applicable regulatory framework. It provides clarity on the development path and scientific regulatory guidance to be followed. It is recommended that this is done before submitting requests for scientific advice/protocol assistance or other discussions with the EMA. ATMP classification also sometimes may be a useful tool for applicants in initiating a tailored dialogue on product development with the regulators.

Presubmission request form

The applicant shall provide information about the product:

Active substance

- Description of the active substance (including starting materials, when relevant)
- Description of any additional substances (e.g. any applicable structural components such as scaffolds, matrices, biomaterials, biomolecules and/or other components)
- Description of the medical device or active implantable medical device (when applicable)

Finished product

- Qualitative and quantitative composition
- Mode of administration
- Pharmaceutical form (use standard term as applicable) and description of the finished product ready for clinical use

Mechanism of action/proposed use

- Claimed mechanism of action
- Properties (including pharmacological, immunological or metabolic, if applicable)
- Proposed use/indication (including therapeutic, prophylactic, diagnostic)

In addition, information on the status of development shall be provided (including the element of manufacturing, quality aspects and outline of the non-clinical and clinical development) where this is relevant for ATMP classification. Applicants should also substantiate their positions on the classification of their product in light of the legal definitions in force.

Essential documents

Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced and serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of GCP and with all applicable regulatory requirements. The essential documents also serve several other important purposes. Filing the essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authorities as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The IMPD, IB and Clinical Study Protocol are described briefly below. For the complete list of essential documents, please see Section 8 of ICH guideline E6 on GCP, available from the ICH website.

Investigational medicinal product dossier (IMPD) IMPD guideline and template

IMPD is the basis for approval of clinical trials by the competent authorities in the EU. The IMPD includes summaries of information relating to the quality, manufacture and control of the investigational medicinal product (IMP). An overall risk-benefit assessment, including reference safety information, and critical analyses of the non-clinical and clinical data in relation to the potential risks and benefits of the proposed study must be included in the IMPD.
The applicant may either provide a stand-alone IMPD or cross-refer to the IB for the pre-clinical and clinical parts of the IMPD.

Investigators brochure (IB) ICH-GCP guidelines for IB (section 7)

The IB is a compilation of the clinical and non-clinical data on the IMP(s) relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration and safety monitoring procedures. The IB also provides an insight for supporting the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information.

Clinical study protocol

The clinical study protocol should comply with the scientific, regulatory, statistical and GCP requirements, see guidelines for GCP (section E6). The protocol describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol also contains the background and rationale for the trial. It is essential to include a detailed flow chart of the trial in the clinical study protocol. Basic advice on the clinical study protocol from Läkemedelsverket (in Swedish).

Clinical study procedure

The procedures for clinical trial planning, application, execution, analysis, reporting and archiving have been outlined on the Clinical Studies Sweden website. This only covers the main applications. You may need to contact other entities in your local county council (i.e. hospitals, local priority advice, pharmacy).

Competent authority

To develop a clinical trial authorisation (CTA), an EudraCT number must first be created. The European clinical trials database (EudraCT) is a database of all clinical trials initiated in the EU from May 2004 onwards. An EudraCT number is a unique identifier for the clinical trial. The application form can be completed and downloaded from the EudraCT website once the EudraCT number has

been created. Detailed information on the CTA procedures (in Swedish) is available on the Läkemedelsverket website.

Ethical review board(s) (Etikprövningsnämnderna (EPN))

Detailed information on the application procedures for ethical review of clinical trials in Sweden (in Swedish and English) is available on the EPN website.

Biobank

According to the Swedish Biobank Act (SFS 2002:297) (in Swedish), human biological specimens collected and/or stored within the healthcare system may be used for research purposes provided that the patient/donor has given his/her consent. The collection and/or use of human samples for research purposes requires approval by the ethical review board for each specific research project/clinical trial. A biobank application is needed for all samples collected specifically for a clinical trial (including routine samples that are collected outside clinical practice), even when the samples are analysed and directly destroyed. For more information, read Biobank Sweden

Radiation protection committee

In the case of clinical trials where the participants are exposed to radiation, these trials shall be approved by a radiation protection committee. An application must be sent to the radiation protection committee in the same region as the decision-making regional ethical review board, Radiation safety application (in Swedish)

4a1. Gene therapy medicinal products (GTMPs)

General

A GTMP is an ATMP which has the following characteristics:

a. it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

AND

b. its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence. GTMPs do not include vaccines against infectious diseases.

The EMA has published a guideline relating to the quality of GTMPs within multidisciplinary guidelines, multidisciplinary: gene therapy

The EMA's scientific guidelines on gene therapy help medicine developers prepare marketing authorisation applications for human medicines. As clinical trials provide a significant proportion of the information required for the marketing authorisation application and approval, these guidelines, where applicable, also lay the groundwork for planning and conducting clinical trials with gene therapy products.

Quality (including manufacturing)

Selected guidelines regarding GTMPs, focusing on quality:

- Scientific requirements for the environmental risk assessment of GTMP: Guideline CHMP/GTWP/125491/06 (PDF)
- Quality, pre-clinical and clinical aspects of GTMPs (currently under revision, latest draft 2015): Guideline CHMP/GTWP/234523/09 (PDF)
- Draft revision on the quality, non-clinical and clinical aspects of GTMPs: Guideline EMA/CAT/80183/2014
- Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells: Guideline CHMP/GTWP/671639/2008 (PDF)

For more specific applications, see the following documents:

- Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells: Guideline 3AB6a
- Development and manufacture of lentiviral vectors: Guideline CPMP/BWP/2458/03 (PDF)
- Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMPs: Guideline CAT/CPWP/686637/2011 (PDF)
- Design modifications of gene therapy medicinal products during development: Reflection paper CAT/GTWP/44236/2009 (PDF)
- Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors: Reflection paper CHMP/GTWP/587488/2007 Rev. 1 (PDF)
- ICH considerations: oncolytic viruses EMEA/CHMP/ICH/607698/2008 (PDF)
- Position statement on Creutzfeldt-Jakob disease and advanced therapy medicinal products: EMA/CHMP/CAT/BWP/353632/2010 (PDF)

Non-clinical (pre-clinical)

Non-clinical studies are designed to support the use of a specific product to treat a specific clinical indication. The non-clinical studies conducted are an important element of the overall development pathway for an IMP and significant for establishing feasibility and reasonable safety of the IMP´s proposed clinical route of administration. Non-clinical studies always should be performed in a relevant species. In the case of GTMP, this includes both the activity of the vector construct in animals and potential differences thereof to humans as well as potential differences in viral tropism between the species.

GTMPs usually comprise both a delivery system (vector, virus, cell) and a gene product. It is important to investigate both the delivery system and the therapeutic gene product, unless otherwise justified. Data obtained with other 'similar' products might be supportive but are, in general, not sufficient to warrant first clinical use.

Studies should be designed and carried out with the aim of establishing the following:

• Pharmacodynamics

'Proof of concept' studies should generate non-clinical evidence supporting the potential clinical effect (i.e. potency assay) or at least the related biological effect/molecular mechanism of action [in vivo and/or in vitro studies to be performed – especially when in vivo relevant disease models are not available].

• Bio-distribution

Studies should provide data on all organs, whether target or not, as recommended in Annex A to the Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99) and include investigations into GTMP persistence, mobilisation and shedding.

• Dose

The target dose and escalation scheme should be determined, considering the intended clinical dosing regimen and the toxicological/pharmacokinetic/pharmacodynamic profile of the GTMP.

• Toxicity

Toxicity studies should be carried out for the whole GTMP construct (delivery system and gene product) using the same dose, route and method of administration as in the clinical protocol, unless otherwise justified. Target organs should be identified in terms of toxicity, safety, biological activity and mutagenesis.

Non-clinical studies required before first clinical use of gene therapy medicinal products

Clinical

First-in-human

When the IMP is being tested for the first time in humans, it is useful to read the following guidelines from the EMA:

- Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (PDF)
- Guideline on requirements for first-in-human clinical trials for potential high-risk medicinal products

Phase I/II trial objectives

The main purpose of a Phase I/II trial is safety evaluation; this includes assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose, but also other issues, such as feasibility of administration and pharmacological activity.

Since the ATMP candidate may in fact have little or no toxicity, it may not be worthwhile using toxicity as an endpoint. Biological outcomes, such as engraftment, transgene expression, optimal biological dose or immune response to a vaccine are alternatives for primary endpoints. Secondary objectives for efficacy measures, either short-term response or longer-term outcomes, should be included for support in the design of later-phase trials.

Feasibility assessments

Feasibility assessments are carried out if specialised devices or novel procedures are required for administration, customised preparation of products, special handling of products (e.g. very short expiration time) or adjunctive therapy. Consideration should be given to designing early-phase trials to identify and characterise any technical or logistical issues in the manufacturing or administration of the product. Such issues may need to be addressed before proceeding with further product development.

Dose exploration

When using gene therapies for life-threatening diseases, some toxicities may be expected and acceptable. In these situations, the main objective might be to identify the maximum tolerated dose, i.e. the highest dose that can be given with acceptable toxicity using a dose-escalation protocol.

For some gene therapies, toxicity is not expected to be substantial in the predicted therapeutic range. In this situation, the objective of dose exploration may be to determine the range of biologically active or optimal effective doses.

In some cases, indicators of potential benefit may plateau above a certain dose such that further dose escalation to reach a maximum tolerated dose may be unnecessary.

Activity assessments

Potential efficacy could be indicated by any of the following short-term responses and longer-term outcomes:

- gene expression
- cell engraftment
- morphologic alterations
- more common measures such as changes in immune function
- tumour shrinkage
- physiological responses to various assessments

Phase III trial objectives

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. The investigational medical product must be in a final stage. These studies are intended to provide an adequate basis for marketing approval.

Important links:

Follow-up of patients administered with gene therapy medicinal products: Guideline CHMP/GTWP/60436/07 (PDF)
Design modifications of gene therapy medicinal products during development: Reflection paper CAT/GTWP/44236/2009 (PDF)

4a2. Somatic cell therapy medicinal products (sCTMPs)

General

sCTMPs contain cells or tissues that have been manipulated to change their biological characteristics or cells or tissues not intended to be used for the same essential functions in the body. They can be used to cure, diagnose or prevent diseases;

An sCTMP has the following characteristics:

a. it contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered; or it contains or consists of cells or tissues that are not intended to be used for the same essential function(s) in the recipient as in the donor;

AND

b. it is presented as having properties for, or is used in or administered to, human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

The EMA's scientific guidelines on cell therapy and tissue engineering help medicine developers prepare marketing authorisation applications for human medicines, where clinical trial documentation plays a crucial role. Multidisciplinary: cell therapy and tissue engineering

Quality (including manufacturing)

Selected guidelines regarding sCTMPs, focusing on quality:

- Human cell-based medicinal products: Guideline CHMP/410869/06 (PDF)
- On potency testing of cell-based immunotherapy medicinal products for the treatment of cancer: Guideline EMA/CHMP/BWP/271475/2006 rev. 1 (PDF)
- Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to ATMPs: Guideline CAT/CPWP/686637/2011 (PDF)
- Creutzfeldt-Jakob disease and advanced therapy medicinal products: Position statement EMA/CHMP/CAT/BWP/353632/2010 (PDF)

For more specific applications, see the following documents:

- Xenogeneic cell-based medicinal products: Guideline CHMP/CPWP/83508/09 (PDF)
- In-vitro cultured chondrocyte containing products for cartilage repair of the knee: Reflection paper CAT/CPWP/568181/2009 (PDF)
- Stem cell-based medicinal products: Reflection paper EMA/CAT/571134/2009 (PDF)

Non-clinical (pre-clinical)

Non-clinical studies are designed to support the use of a specific product to treat a specific clinical indication. The non-clinical studies conducted are an important element of the overall development pathway for an IMP and significant for establishing feasibility and reasonable safety of the IMP's proposed clinical route of administration. The overall objectives for a sufficient non-clinical programme for an sCTMP may include:

- Establishing biological plausibility
- Identifying biologically active dose levels

- Selecting the potential starting dose level, dose-escalation schedule and dosing regimen for clinical trials
- Establishing feasibility and reasonable safety of the investigational product's proposed clinical route of administration
- Supporting patient eligibility criteria
- Identifying physiological parameters which can guide clinical monitoring
- Identifying potential public health risks (e.g. to the general public, caregivers, family members, close contacts (for example co-workers) and intimate contacts)

The resulting data from pre-clinical studies should address these objectives in order to guide the design of early-phase clinical trials, as well as to establish a platform for the conduct of future pre-clinical studies that may be needed to support later phases of product development.

Non-clinical studies using cell-based medicinal products should be performed in relevant species. Considering the nature of these products this is specifically challenging. It is always recommended to seek the advice of the relevant authorities when selecting the species for non-clinical studies, especially pivotal safety studies. Homologous products could be used, however in such cases bridging data to the human product is of the utmost importance.

ATMPs and cell-based ATMPs in particular present additional challenges that should be addressed, such as:

- Cell survival status following delivery
- Cell migration or trafficking to non-target sites
- Cell differentiation into undesired cell types
- Development of an immune response to the cells
- Uncontrolled proliferation or tumorigenicity

The EMA has a set of scientific guidelines on the non-clinical testing of a medicinal product; these guidelines are provided for:

- Environmental risk assessment
- Non-clinical development
- Pharmacology and safety pharmacology
- Toxicology

ATMPs differ from traditional medicinal products and some aspects of the guidelines may not be applicable. However, in such cases a rationale and risk assessment for not following the guidelines shall be available.

Important link:

Setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC, Directive 2002/98/EC

Clinical

First-in-human

When the IMP is being tested for the first time in humans, it is useful to read the following guidelines from the EMA:

- Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (PDF)
- Guideline on requirements for first-in-human clinical trials for potential high-risk medicinal products

Phase I/II trial objectives

The main purpose of a Phase I/II trial is safety evaluation; this includes assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose, but also other issues, such as feasibility of administration and pharmacological activity.

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Feasibility assessments

Feasibility assessments are carried out if specialised devices or novel procedures are required for administration, customised preparation of products, special handling of products (e.g. very short expiration time) or adjunctive therapy. Consideration should be given to designing early-phase trials to identify and characterise any technical or logistical issues in the manufacturing or administration of the product. Such issues may need to be addressed before proceeding with further product development.

Dose exploration

When using cell therapies for life-threatening diseases, some toxicities may be expected and acceptable. In these situations, the main objective might be to identify the maximum tolerated dose (MTD), i.e. the highest dose that can be given with acceptable toxicity using a dose-escalation protocol.

For some cell therapies, toxicity is not expected to be substantial in the predicted therapeutic range. In this situation, the objective of dose exploration may be to determine the range of biologically active or optimal effective doses.

In some cases, indicators of potential benefit may plateau above a certain dose such that further dose escalation to reach a maximum tolerated dose may be unnecessary.

Activity assessments

Potential efficacy could be indicated by any of the following short-term responses and longer-term outcomes:

- cell engraftment
- morphologic alterations
- more common measures such as changes in immune function
- tumour shrinkage
- physiological responses to various assessments

Phase III trial objectives

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population.

These studies are intended to provide an adequate basis for marketing approval.

4a3. Tissue engineered products (TEPs)

General

TEPs contain cells or tissues that have been modified so they can be used to repair, regenerate or replace human tissue.

A TEP has the following characteristics:

a. it contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered; or it contains or consists of cells or tissues that are not intended to be used for the same essential function(s) in the recipient as in the donor

AND

b. it is presented as having properties for, or is used in or administered to, human beings with a view to regenerating, repairing or replacing a human tissue

Quality (including manufacturing)

Selected guidelines regarding TEPs, focusing on quality:

- Human cell-based medicinal products: Guideline EMEA/CHMP/410869/2006
- Certain technical requirements for the coding of human tissues and cells: Directive 2015/565 EC

Non-clinical (pre-clinical)

Non-clinical studies are designed to support the use of a specific product to treat a specific clinical indication. The non-clinical studies conducted are an important element of the overall development pathway for an investigational product. They facilitate the establishment of feasibility and reasonable safety (case-by-case according to risk assessment) of the investigational product's proposed clinical route of administration. The overall objectives for a sufficient pre-clinical programme for a TEP may include:

- Establishing biological plausibility
- Identifying biologically active dose levels
- Selecting the potential starting dose level, dose-escalation schedule and dosing regimen for clinical trials
- Establishing feasibility and reasonable safety of the investigational product's proposed clinical route of administration (ROA)
- Supporting patient eligibility criteria
- Identifying physiological parameters which can guide clinical monitoring
- Identifying potential public health risks (e.g. to the general public, caregivers, family members, close contacts (for example co-workers) and intimate contacts)

The resulting data from pre-clinical studies should address these objectives in order to guide the design of early-phase clinical trials, as well as to establish a platform for the conduct of future pre-clinical studies that may be needed to support later phases of product development.

Non-clinical studies should be performed in relevant species. Considering the nature of these products this is specifically challenging. It is always recommended to seek the advice of the relevant authorities when selecting the species for non-clinical studies, especially pivotal safety studies.

Homologous products could be used, however in such cases bridging data to the human product is of the utmost importance.

ATMPs and cell-based ATMPs in particular present additional challenges that should be addressed, such as:

- Cell survival status following delivery
- Cell migration or trafficking to non-target sites
- Cell differentiation into undesired cell types
- Development of an immune response to the cells
- Uncontrolled proliferation or tumorigenicity

The EMA has a set of scientific guidelines on the non-clinical testing of a medicinal product; these guidelines are provided for:

ATMPs differ from traditional medicinal products and some aspects of the guidelines may not be applicable. However, in such cases a rationale and risk assessment for not following the guidelines shall be available.

- Environmental risk assessment
- Non-clinical development
- Pharmacology and safety pharmacology
- Toxicology

Clinical

First-in-human

When the IMP is being tested for the first time in humans, it is useful to read the following guidelines from the EMA:

- Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (PDF)
- Guideline on requirements for first-in-human clinical trials for potential high-risk medicinal products

Phase I/II trial objectives

The main purpose of a Phase I/II trial is safety evaluation; this includes assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose (if applicable), but also other issues, such as feasibility of administration and pharmacological activity. Since the TEP candidate may in fact have little or no toxicity, other endpoints such as time to relapse, rejection and infections may be more useful. Clinical efficacy endpoints, as defined in specific guidance for the studied indication or disease, form the basis for the clinical evaluation of TEPs. Additional cell- and tissue-specific endpoints may be required such as biochemical, morphological, structural and functional parameters, which are relevant for the targeted therapeutic claim. These endpoints can be used as co-primary or secondary variables and are expected to support the clinical primary efficacy variable. Examples of endpoints should be related to conditions treated.

The tissue functionality and structural aspects of the regenerated, repaired and/or replaced tissue as well as its persistence in the human body are specific attributes of TEPs that should be considered when choosing the clinical endpoints.

Feasibility assessments

Feasibility assessments are carried out if specialised devices or novel procedures are required for administration, customised preparation of products, special handling of products (e.g. very short expiration time) or adjunctive therapy. Consideration should be given to designing early-phase trials to identify and characterise any technical or logistical issues in the manufacturing or administration of the product. Such issues may need to be addressed before proceeding with further product development.

Dose exploration

To the extent possible, the dose selection (i.e. cell density or concentration of main constituents) should be based on findings from quality and non-clinical product development. Dose finding studies in the clinical setting should be conducted where feasible. However, the risks relating to high or suboptimal cell numbers should be considered and addressed. Limitations of the available amount of cells/tissue in the TEP (e.g. due to autologous donation, manufacturing procedure) may lead to the use of variable doses on comparable sizes of defects. In these cases, the variable dosing should be justified and the correlation of the dose with the clinical efficacy should be carefully recorded and reported.

Phase III trial objectives

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. The investigational medical product must be in a final stage. These studies are intended to provide an adequate basis for marketing approval.

Important link:

Clinical aspects relating to tissue engineered products: Reflection paper EMA/CAT/573420/2009 (PDF)

4a4. Combined ATMPs

General

Combined ATMPs contain one or more medical devices as an integral part of the medicine. An example of this is cells embedded in a biodegradable matrix or scaffold.

A combined ATMP must fulfil either (a and b) or (a and c):

a) it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC
b) its cellular or tissue part must contain viable cells or tissues
c) its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to

Quality (including manufacturing)

For combined ATMPs, it is important to include the device in the validation process:

- Validation of the cell culture process with respect to the integrity of cells/scaffold
- Effect of the device on cell growth and activity
- Effect of cells on device function and integrity
- Characterisation and testing of the cell-device combination
- Impurities and degradation products from device component
- CE mark of device component, if possible

Selected documents and guidelines regarding combined ATMPs, focusing on quality:

- ISO 13485; a standard for quality management systems for medical devices (available for purchase sis.se)
- Environmental risk assessment of medicinal products for human use: Guideline CPMP/SWP/4447/00 (PDF)
- Community code relating to medicinal products for human use: Directive 2001/83/EC
- Supplementary protection certificate for medicinal products: Regulation 469/2009 EC
- The medical device/devices which is/are part of the product shall meet the essential requirements laid down in Annex 1 to Directive 93/42/EEC (for medical devices: Harmonised standards for medical devices) or Annex 1 to Directive 90/385/EEC (for active implantable medical devices: Harmonised standards for active implantable medical devices).
- Commission Regulation No 722/2012 concerning particular requirements as regards the requirements laid down in Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin: Requirements for the medical device if utilising tissues of animal origin

Non-clinical (pre-clinical)

Non-clinical studies are designed to support the use of a specific product to treat a specific clinical indication. The non-clinical studies conducted are an important element of the overall development pathway for an investigational product. They facilitate the establishment of feasibility and reasonable safety (case-by-case according to risk assessment) of the investigational product's proposed clinical route of administration. The overall objectives for a sufficient pre-clinical programme for a combined ATMP may include:

- Establishing biological plausibility
- Identifying biologically active dose levels
- Selecting the potential starting dose level, dose-escalation schedule and dosing regimen for clinical trials
- Establishing feasibility and reasonable safety of the investigational product and its proposed clinical route of administration (ROA)
- Supporting patient eligibility criteria
- Identifying physiological parameters which can guide clinical monitoring
- Identifying potential public health risks (e.g. to the general public, caregivers, family members, close contacts (for example co-workers) and intimate contacts)

The resulting data from pre-clinical studies should address these objectives in order to guide the design of early-phase clinical trials, as well as to establish a platform for the conduct of future pre-clinical studies that may be needed to support later phases of product development.

Non-clinical studies should be performed in relevant species. Considering the nature of these products this is specifically challenging. It is always recommended to seek the advice of the relevant authorities when selecting the species for non-clinical studies, especially pivotal safety studies. Homologous products could be used, however in such cases bridging data to the human product is of the utmost importance.

ATMPs and cell-based ATMPs in particular present additional challenges that should be addressed, such as:

- Cell survival status following delivery
- Cell migration or trafficking to non-target sites
- Cell differentiation into undesired cell types
- Development of an immune response to the cells
- Uncontrolled proliferation or tumorigenicity

Combined ATMPs usually comprise both a delivery system and an ATMP. It is important to investigate both the delivery system and the ATMP, unless otherwise justified.

The EMA has a set of scientific guidelines on the non-clinical testing of a medicinal product; these guidelines are provided for:

- Environmental risk assessment
- Non-clinical development
- Pharmacology and safety pharmacology
- Toxicology

ATMPs differ from traditional medicinal products and some aspects of the guidelines may not be applicable. However, in such cases a rationale and risk assessment for not following the guidelines shall be available.

Clinical

First-in-human

When the IMP is being tested for the first time in humans, it is useful to read the following guidelines from the EMA:

- Strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products (PDF)
- Guideline on requirements for first-in-human clinical trials for potential high-risk medicinal products

Phase I/II trial objectives

The main purpose of a Phase I/II trial is safety evaluation; this includes assessment of the nature and frequency of potential adverse reactions and an estimation of the relationship to dose, but also other issues, such as feasibility of administration and pharmacological activity.

Clinical efficacy endpoints, as defined in specific guidance for the studied indication or disease, form the basis for the clinical evaluation of any ATMPs, including combined ATMPs. Additional cell- and tissue-specific endpoints may be required such as biochemical, morphological, structural and functional parameters, which are relevant for the targeted therapeutic claim. These endpoints can be used as co-primary or secondary variables and are expected to support the clinical primary efficacy variable.

Feasibility assessments

Consideration should be given to designing early-phase trials to identify and characterise any technical or logistical issues in the manufacturing or administration of the product. Such issues may need to be addressed before proceeding with further product development.

Dose exploration

To the extent possible, the dose selection (i.e. cell density or concentration of main constituents) should be based on findings from quality and non-clinical product development. Dose finding studies in the clinical setting should be conducted where feasible. However, the risks relating to high or suboptimal cell numbers should be considered and addressed. Limitations of the available amount of cells/tissue (e.g. due to autologous donation, manufacturing procedure) may lead to the use of variable doses on comparable sizes of defects. In these cases, the variable dosing should be justified and the correlation of the dose with the clinical efficacy should be carefully recorded and reported.

Phase III trial objectives

Phase III usually is considered to begin with the initiation of studies in which the primary objective is to demonstrate or confirm therapeutic benefit. Studies in Phase III are designed to confirm the preliminary evidence accumulated in Phase II that a drug is safe and effective for use in the intended indication and recipient population. The investigational medical product must be in a final stage. These studies are intended to provide an adequate basis for marketing approval.

4b. Hospital exemption (HE)

Definition

The purpose of the Hospital Exemption (HE) LVFS_2011-3 (in Swedish) is to provide an ATMP without marketing authorisation. HE is to be used in hospital when there is high unmet medical need and for an individual patient under the exclusive professional responsibility of a medical practitioner. This may include any ATMP manufactured under GMP:

- On a non-routine basis
- According to specific quality standards
- On an individual patient basis
- Used in the same EU member state.

Legal framework

- Manufacturing of the HE must be authorised by the Läkemedelsverket and according to GMP.
- Tissue establishment authorisation: LVFS_2011-4 (in Swedish) LVFS_2008-12 (in Swedish)
- Manufacturing authorisation for HE: LVFS_2011-3 (in Swedish)
- A qualified person (QP) is needed; the necessary qualifications and responsibilities are described in LVFS 2004:7 and also in GMP vol. 4 Annex 16
- Any adverse events that occur during a treatment under HE must be reported to Läkemedelsverket according to LVFS 2012:14 (in Swedish)
- Ethical permission is not required but *strongly recommended*. Detailed information on the application procedures for ethical review of clinical trials in Sweden (in Swedish and English) is available on the EPN website.