CATAPULT
Cell and Gene Therapy

ADVANCED THERAPY MEDICINAL PRODUCTS (ATMPs)

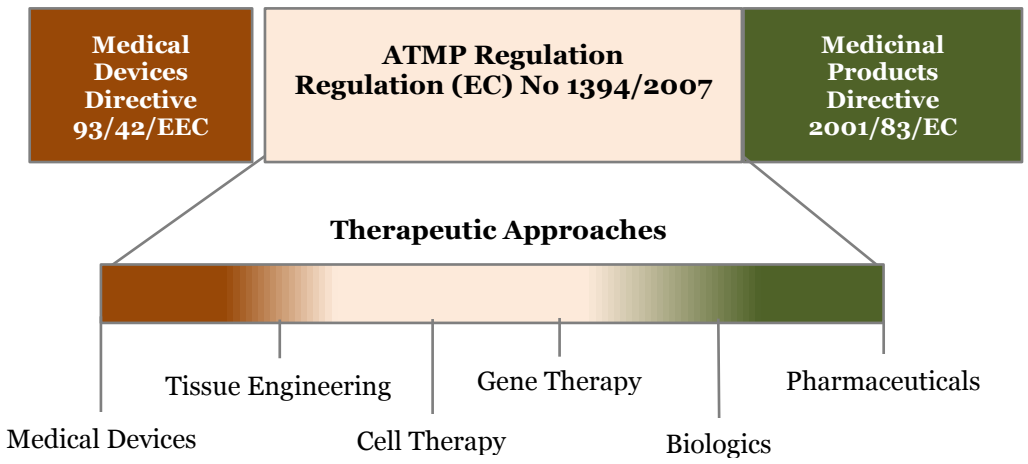
LEGISLATION & GUIDANCE

This non-exhaustive list of directives, regulations and guidance is intended to provide a reference of information for ATMP developers within the European Union (EU) who are interested in commercialising cell, gene and tissue-engineered therapies. The legal framework for marketing authorisation in Europe is based on various legislative texts which separate medicinal products, medical devices and associated procedures into their own distinct areas with separate regulations and competent authorities. In practice, many of these areas overlap which can result in a number of directives and regulatory agencies for a single product – this is particularly relevant for ATMPs (see figure below).

Importantly, the essential requirements for ATMPs developed for marketing authorisation are not different from those which already exist for small molecule drugs and protein therapeutics. Developers must be able to demonstrate a product with consistent quality and few (and safe) levels of impurities. In addition, there must be evidence of a carefully considered 'risk-based' approach towards the clinic, evaluating key safety concerns and how these are controlled or mitigated. Finally, any potential toxicities must be balanced against the treatment of the disease or symptoms (i.e. efficacy). Overall, the data expected by a regulator will be based on the unique scientific and clinical considerations of your product.

Legislation which is not specific for ATMPs has been excluded from this list. Further information can be found on the website for European Law (http://eur-lex.europa.eu/homepage.html) and the European Medicines Agency (http://www.ema.europa.eu/ema/).

Rationale for dedicated ATMP Regulation in the EU



ATMP Legislation and Guidance	
Reference	**Title**
Regulation (EC) **No 1394/2007**	**Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004**
Reflection Paper **EMA/CAT/600280/2010 rev.1**	**Classification of advanced therapy medicinal products** *This reflection paper has been updated to reflect the current thinking of the Committee on Advanced Therapies (CAT) on substantial manipulation and non-homologous use. Additional changes have been implemented throughout the text to clarify the existing concepts, e.g. the demarcation between vaccines against infectious diseases and gene-therapy medicinal products and the criteria for combined advanced-therapy medicinal products*
Guideline **EMEA/149995/2008**	**Safety and efficacy follow-up - risk management of advanced therapy medicinal products** *This guideline describes a framework of regulatory requirements applicable to all ATMPs. Specific provisions for gene-therapy, cell-therapy and tissue-engineered products continue to be included in product type-specific guidelines.*
Guideline **CAT/CPWP/686637/2011**	**Risk-based approach according to Annex I, part IV of Directive 2001/83/EC applied to Advanced Therapy Medicinal Products** *This guideline describes the intention of the risk-based approach and details its methodological application. The methodology is based on the identification of risks and associated risk factors of an advanced-therapy medicinal product and the establishment of a specific profile for each risk. With the use of the identified risk profile the applicant shall justify the extent of data presented in the various sections of the marketing-authorisation application dossier.*

Guideline **EMA/CAT/216556/2017**	**Development of non-substantially manipulated cell-based advanced therapy medicinal products: flexibility introduced via the application of the risk-based approach** *This document aims to illustrate some of the possibilities and limitations of the risk-based approach using the example of an ATMP based on cells that have not been subjected to substantial manipulation and that are not intended for the same essential function: a de-novo development of autologous bone marrow or peripheral blood CD34+ cells for treatment of acute myocardial infarction.*
Reflection Paper **CAT/571134/09**	**Stem cell-based medicinal products** *This reflection paper is relevant to all medicinal products using stem cells as starting material. The final products may consist of terminally differentiated cells derived from stem-cells, of undifferentiated stem cells or even of a mixture of cells with varying differentiation profile. This document addresses manufacturing, characterisation and quality control as well as and non-clinical and clinical development of stem cell based products.*
Reflection paper **CAT/CPWP/568181/2009**	**In-vitro cultured chondrocyte containing products for cartilage repair of the knee** *This document addresses specific points related to medicinal products containing in vitro cultured autologous chondrocytes intended for the repair of cartilage lesions of the knee. It supplements the guideline on human cell-based medicinal products.*
CHMP/CAT Position Statement **EMA/CHMP/CAT/BWP/353632/2010**	**Creutzfeldt-Jakob disease and advanced therapy medicinal products** *The composition of ATMPs may include components of human origin (either as active ingredient, excipients, or raw materials used in their manufacture) and, therefore, the risk of transmitting CJD or vCJD agents has to be considered*
Reflection paper **EMA/CAT/573420/2009**	**Clinical aspects related to tissue engineered products** *This document provides specific guidance on clinical testing for tissue engineered products (TEPs). It is intended as a supplement to the guideline on human cell-based medicinal products and gives current thinking regarding clinical aspects on TEPs.*

Guideline **EMEA/CHMP/CPWP/83508/2009**	**Xenogeneic cell-based medicinal products** *This document addresses the scientific requirements for medicinal products that contain viable animal cells or tissues as an active substance (xenogeneic cell-based medicinal products). It provides general principles for the development and assessment of xenogeneic cell-based products without prejudice to medical practice or national legislation, which may be applicable.*
Guideline **CHMP/410869/06**	**Human cell-based medicinal products** *This document addresses development, manufacturing and quality control as well as and non-clinical and clinical development of cell-based medicinal products. It covers somatic cell therapy medicinal products and tissue engineered products.*
Guideline **CHMP/BWP/271475/06**	**Potency testing of cell based immunotherapy medicinal products for the treatment of cancer** *The potency (i.e., the quantitative measure of biological activity) of cell based immunotherapy products can be measured using in vivo or in vitro tests. An appropriately validated potency assay should be based on a defined biological effect as close as possible to the mechanism(s) of action/clinical response. Surrogates for potency may be developed to demonstrate biological activity of the test sample. Development and validation of such assays for cell based immunotherapy products need special considerations. This document represents CHMP's current thinking on these issues.*
Regulation (EC) **No 668/2009**	**Quality & non-clinical safety certification of ATMPs for SMEs** *Commission of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to advanced therapy medicinal products developed by micro, small and medium-sized enterprises*
Guideline **Eudralex Volume 4 (GMP)**	**Part IV - GMP requirements for Advanced Therapy Medicinal Products** *Eudralex Volume 4 covering the rules governing medicinal products in the European Union contains guidance for the interpretation of the principles and guidelines of good manufacturing practices for medicinal products for human and veterinary laid down in Commission Directives 91/356/EEC, as amended by Directive 2003/94/EC, and 91/412/EEC*

Reflection paper **CAT/190186/2012**	**Management of clinical risks deriving from insertional mutagenesis** *This document discusses the factors contributing to genotoxicity of vector integration, the strategies to reduce the risk associated to insertional mutagenesis and the assays to evaluate vector oncogenesis at the pre-clinical and clinical level.*
Guideline **EMEA/CHMP/GTWP/60436/2007**	**Follow-up of patients administered with gene therapy medicinal products** *This document addresses specific aspects of the active clinical follow-up of patients administered with gene therapy medicinal products in order to detect signals of early or delayed adverse reactions, to prevent clinical consequences of such reactions, to ensure timely treatment and to gain information on the long-term safety and efficacy of the intervention.*
Procedural Advice **EMA/354785/2010**	**Procedural advice on the evaluation of combinedadvanced therapy medicinal products and the consultation of notified bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007** *Regulation (EC) No 1394/2007 states that ATMPs may incorporate medical devices or active implantable medical devices as defined in Directive 93/42/EEC and 90/385/EEC respectively. In order to ensure an appropriate level of quality and safety, those devices should meet the essential requirements laid down in the relevant Directive. A Notified Body (NB) for medical devices may be or may have been involved in the assessment of the medical device part of a combined ATMP. As the CAT prepares the draft opinion on a combined ATMP, it will therefore be this Committee who primarily interacts with a NB in the context of the procedure described in this document.*
Q&A Document **EMA/CHMP/GTWP/212377/08**	**Questions and answers on gene therapy** *This document addresses questions on matters related to the development of gene therapy medicinal products. It provides harmonized position on issues that can be subject to different interpretation or require clarification, typically arising from discussions during briefing meetings with stakeholders.*

Guideline **CHMP/GTWP/125491/06**	**Scientific requirements for the environmental risk assessment of gene therapy medicinal products** *This document provides guidance on the environmental risk assessment of GMO-containing gene therapy medicinal products, as required for marketing authorisation under the centralised procedure. It aims to facilitate the application of the methodology laid down in the Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.*
Reflection paper **EMA/CAT/GTWP/44236/2009**	**Design modifications of gene therapy medicinal products during development** *This document presents regulatory considerations given for specific gene therapy medicinal products where the characteristics have been changed at various stages during clinical development. It gives some insight into the types of studies that are likely to be required in an application dossier to support the modification in the product design introduced during development.*
Reflection paper **CHMP/GTWP/587488/07**	**Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors** *This document aims to discuss quality, non-clinical and clinical issues that should be considered during the development of medicinal products derived from adeno-associated viral vectors. It indicates requirements that might be expected at the time of a marketing authorisation application.*
Guideline **EMEA/CHMP/ICH/607698/2008**	**ICH Considerations: Oncolytic Viruses** *This document describes the general principles for the manufacturing, characterisation, non-clinical and clinical testing of medicinal products based on oncolytic viruses.*
Guideline **CAT/CHMP/GTWP/671639/2008** *Currently under revision*	**Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells** *This document defines scientific principles and provides guidance for the development and evaluation of* medicinal products *containing genetically modified cells intended for use in humans and presented for* marketing authorisation.
Guideline **EMEA/CHMP/GTWP/125459/2006**	**Non-clinical studies required before first clinical use of gene therapy medicinal products** *This document defines scientific principles and provides guidance to applicants developing gene therapy medicinal products (GTMPs). It focuses on the non-clinical studies required before the first use of a GTMPs in human subjects.*

Guideline **EMEA/273974/2005**	**Non-clinical testing for inadvertent germline transmission of the gene transfer vectors** *This document provides guidance on non-clinical inadvertent germline transmission testing needed to support clinical development of gene transfer medicinal products consisting of or containing replication-incompetent vectors, genetically modified viruses or so-called naked nucleic acids directly administered to humans.*
Guideline **CHMP/ICH/469991/2006**	**General principles to address the risk of inadvertent germline integration of gene therapy vectors** *This document identifies general principles for investigating and addressing risks for inadvertent germline integration. It provides considerations to minimise this potential risk in humans enrolled in clinical trials. This document applies to gene therapy vectors and could also apply to oncolytic viruses.*
Guideline **EMEA/CHMP/ICH/449035/2009**	**General principles to address virus and vector shedding** *This document provides recommendations for designing non-clinical and clinical virus/vector shedding studies. In particular, it emphasizes the analytical assays used for detection and considerations for the sampling profiles and schedules in both non-clinical and clinical studies. The interpretation of non-clinical data and its use in designing clinical studies is also within the scope of this paper, as well as the interpretation of clinical data in assessing the need for virus/vector transmission studies.*
Guideline **EMEA/CHMP/BWP/473191/2006**	**Guideline on environmental risk assessments for medicinal products consisting of, or containing, genetically modified organisms (GMOs)** *This document explains the application of the centralised procedure to marketing authorisation (MA) applications for medicinal products consisiting of or containing genetically modified organisms. It outlines both the procedural issues affecting applications for MA for these products and the information related to the environmental risk assessment which should be included in the applications.*
Directive (EC) **2004/23/EC**	**Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells**
Directive (EC) **2002/98/EC**	**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**