Handbook about Regulatory Guidelines and Procedures for the Preclinical and Clinical Stages of Advanced Therapy Medicinal Products (ATMPs)

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<td>ABM</td>
<td>Agence de Biomédecine</td>
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<tr>
<td>ACI</td>
<td>Autologous chondrocyte implantation</td>
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<td>AIMD</td>
<td>Active implantable medical devices</td>
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<tr>
<td>ANSM</td>
<td>Agence nationale de sécurité due medicament et des produits de santé</td>
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<tr>
<td>ATIMP</td>
<td>Advanced therapy investigational medicinal product</td>
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<td>ATMP</td>
<td>Advanced therapy medicinal product</td>
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<tr>
<td>CAT</td>
<td>Committee for Advanced Therapies</td>
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<td>CBER</td>
<td>Center for Biologics Evaluation and Research</td>
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<td>CBMP</td>
<td>Cell-based medicinal products</td>
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<tr>
<td>CDER</td>
<td>Center for Drug Evaluation and Research</td>
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<td>CDRH</td>
<td>Center for Devices and Radiological Health</td>
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<td>CHMP</td>
<td>Committee for Medicinal Products for Human Use</td>
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<tr>
<td>CMDh</td>
<td>Coordination Group for Mutual Recognition and Decentralised Procedures – Human</td>
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<tr>
<td>COMP</td>
<td>Committee on Orphan Medicinal Products</td>
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<td>CPWP</td>
<td>Cell-based products working party (at the EMA)</td>
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<tr>
<td>CTA</td>
<td>Clinical trial application</td>
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<tr>
<td>CTD</td>
<td>Common Technical Document</td>
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<tr>
<td>DG</td>
<td>Directorate General</td>
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<tr>
<td>EC</td>
<td>European Commission; European Community</td>
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<td>EDQM</td>
<td>European Directorate for the Quality of Medicines and Healthcare</td>
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<td>EEA</td>
<td>European Economic Area</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>EU</td>
<td>European Union</td>
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<tr>
<td>EUROCET</td>
<td>European Registry for Organs, Tissues and Cells</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>FDCA</td>
<td>Food, Drug and Cosmetic Act</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
</tr>
<tr>
<td>GHTF</td>
<td>Global Harmonization Task Force</td>
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<tr>
<td>GMP</td>
<td>Good manufacturing practice</td>
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<tr>
<td>GT</td>
<td>Gene therapy</td>
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<td>GTMP</td>
<td>Gene therapy medicinal product</td>
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<tr>
<td>GTWP</td>
<td>Gene therapy working party (at the EMA)</td>
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<tr>
<td>HCT/Ps</td>
<td>Human cells, tissues and cellular &amp; tissue-based products</td>
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<tr>
<td>IB</td>
<td>Investigator’s brochure</td>
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<tr>
<td>ICH</td>
<td>International Conference on Harmonisation of Technical Requirements for</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>ICRS</td>
<td>International Cartilage Research Society</td>
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<td>IMDRF</td>
<td>International Medical Device Regulators Forum</td>
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<tr>
<td>IMP</td>
<td>Investigational medicinal product</td>
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<tr>
<td>ITF</td>
<td>Innovation Task Force</td>
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<tr>
<td>IVD</td>
<td>In vitro diagnostic</td>
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<tr>
<td>KOOS</td>
<td>Knee injury and Osteoarthritis Outcome Score</td>
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<tr>
<td>LPLD</td>
<td>Lipoprotein lipase deficiency</td>
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<tr>
<td>MA</td>
<td>Marketing authorization</td>
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<td>MAA</td>
<td>Marketing authorization application</td>
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<td>MAH</td>
<td>Marketing authorization holder</td>
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<td>MDD</td>
<td>Medical Device Directive</td>
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<td>MoA</td>
<td>Mode of action</td>
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<td>MP</td>
<td>Medicinal product</td>
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<tr>
<td>NANDO</td>
<td>New Approach Notified and Designated Organisations</td>
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<tr>
<td>NB</td>
<td>Notified body</td>
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<tr>
<td>NCA</td>
<td>National competent authorities</td>
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<tr>
<td>NTA</td>
<td>Notice to Applicants</td>
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<tr>
<td>OCTGT</td>
<td>Office of Cellular, Tissue and Gene Therapies (at CBER)</td>
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<tr>
<td>PAP-GM-CSF</td>
<td>Prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor</td>
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<tr>
<td>Ph.Eur.</td>
<td>European Pharmacopoeia</td>
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<td>PHS Act</td>
<td>Public Health Service Act</td>
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<tr>
<td>PIP</td>
<td>Paediatric investigational plan</td>
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<tr>
<td>PRAC</td>
<td>Pharmacovigilance Risk Assessment Committee</td>
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<tr>
<td>Q&amp;A</td>
<td>Question and answer</td>
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<tr>
<td>QPPV</td>
<td>Qualified person for pharmacovigilance</td>
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<tr>
<td>RMP</td>
<td>Risk management plan</td>
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<tr>
<td>SAWP</td>
<td>Scientific Advice Working Party</td>
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<tr>
<td>SCT</td>
<td>Somatic cell therapy</td>
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<td>SCTMP</td>
<td>Somatic cell therapy medicinal product</td>
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<tr>
<td>SEC</td>
<td>Single European Code</td>
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<tr>
<td>SME</td>
<td>Small and medium-sized enterprise</td>
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<tr>
<td>SmPC</td>
<td>Summary of product characteristics</td>
</tr>
<tr>
<td>TE</td>
<td>Tissue establishment</td>
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<tr>
<td>TEP</td>
<td>Tissue-engineered product</td>
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Introduction

The advances in science and technology – especially in cellular and molecular biotechnology – have introduced new types of innovative medicinal products whose pharmacological activity is derived from modified somatic cells (somatic cell therapy, SCT) and tissues (tissue-engineered products, TEP) or genes (gene therapy, GT). While the general regulatory framework and legal requirements for medicinal products equally applies to these so-called advanced therapy medicinal products (ATMP), their unique complexity and specific nature made it necessary to draft legislation and guidance specifically tailored towards cell- and gene-based medicinal products.

On 30 October 2007 the European Council formally adopted the Regulation on Advanced Therapy Medicinal Products (Regulation (EC) No 1394/2007)\(^1\), which has been effective in the European Union since 30 December 2008. The main goal of the regulation is to facilitate the access of ATMP to the EU market, to ensure their free movement within Europe as well as to foster the competitiveness of European companies in the field while at the same time safeguarding the health of patients.

The regulation applies to advanced therapies manufactured by industrial methods and that are intended to be placed on the market in EU Member States. Excluded are products that are custom-made for an individual patient based on a medical prescription and administered in a hospital setting under the responsibility of a qualified medical practitioner (so-called hospital exemption). In these cases national legislation apply (see Section II, 7 Hospital Exemptions).

In addition, a number of regulatory documents (guidelines, reflection papers and Question-and-Answer (Q&A) documents) have been published to clarify the provisions of the regulation in general and their procedural implementation in particular.

Another characteristic that distinguishes ATMPs from traditional small molecules and to some extent also from biological or biotechnology-derived products is that “big pharma” or multi-national pharmaceutical companies rarely develop ATMPs. Approximately 60% of ATMPs developed in the EU originate from so-called “non-commercial sponsors”, with another 38% developed by small to medium-sized enterprises (SME).

Consequently, the regulatory requirements for this complex and multifaceted class of medicinal products has to be addressed, implemented and adhered to by professionals with the least experience and resources to implement and comply with these regulations. This fact is being recognized by the legislator and regulators who have put in place a number of provisions to facilitate the development and guide manufacturers of this advanced therapy products.

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\(^1\) Published in the Official Journal on 10/11/2007
About this book

This handbook aims to provide a comprehensive guide to the existing regulatory landscape and framework for the development and licensing of ATMP.

The objectives of this book are

- To outline the requirements and processes for marketing authorization of new ATMPs in the EU;
- To provide information about the main differences between the regulatory requirements for different types of ATMPs;
- To provide information about the main differences between the regulatory requirements of traditional drugs and ATMPs;
- To provide an overview of the preclinical and clinical development of ATMPs, the requirements and objectives, in order to understand/estimate the time and resources needed in each phase of development;
- To provide guidance to sponsors and developers of ATMPs for the establishment of initial contacts with regulatory agencies.

This book provides support for:

- Scientists working in ATMP-related technologies and intended for the EU market;
- Companies promoting new ATMPs products in the EU without previous experience in this type of medicinal products.

The chapters of this handbook have been written to raise awareness of and give context to the overall regulatory framework that specifically applies to ATMPs. Aspects relating to medicinal products in general are briefly summarized in the supplements to this manual; the information is intended more as a general reference since a detailed discussion of all these regulatory topics goes beyond the scope of this book.
Section I. – Definition and Classification of ATMPs in Europe

In order to understand the unique features and specific requirements of advanced therapy medicinal products (ATMPs) and their place in the EU regulatory framework, this first section will introduce the legal definitions of various types of healthcare products. Cases of combination products as well as borderline considerations will also be presented.

1. Definition of Medicinal Products

Medicinal products in general are defined in the so-called Community code relating to medicinal products for human use (Directive 2001/83/EC), or short “the Directive”:

   Article 1, Medicinal product:

   (a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or

   (b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

This means that the primary mode of action of a medicinal product (also referred to as drug or biological) within the human body is achieved by pharmacological, immunological or metabolic means. Conventional medicinal products are made from chemicals (also referred to as small molecule drugs) or proteins (biologics or biotechnology-derived drugs).

Medicinal products are regulated by extensive pharmaceutical legislation, which today is widely harmonized across the Member States through EU regulations, directives and guidelines.

2. Definition of Medical Devices

In contrast to medicinal products, medical devices are healthcare products, which exert their principal mode of action by physical means. These can be assisted by pharmacological, immunological or metabolic activities, i.e. through the combination with a drug; however, in order to be classified as a medical device the intended purpose of the product must be primarily achieved by a physical mode of action.


The official definition of a medical device is given in Article 1 of the MDD:

   (a) ‘Medical device’ means any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by
its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

— diagnosis, prevention, monitoring, treatment or alleviation of disease,
— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,
— investigation, replacement or modification of the anatomy or of a physiological process,
— control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

Medical devices are an extremely diverse and heterogeneous group of products, ranging from tongue depressors or clinical thermometers over diagnostic lab tests and imaging devices to artificial heart valves, prosthetic limbs and pacemakers.

The processes required for placing medical devices on the market are significantly different from medicinal products. A detailed description of the regulatory framework for medical devices is beyond the scope of this handbook. However, in essence, devices have to show conformity with so-called essential requirements outlined in applicable directives. Notified bodies in each Member State are designated to carry out conformity assessment according to a directive. Of note, no centralized/pan-European procedure exists for these assessments.

3. Definition of ATMPs

As mentioned, conventional drugs usually contain chemicals or proteins as active ingredients (=active substances). However, recent advances in science and technology have led to the emergence of medicinal products consisting of genes or cells. While these products can also be subsumed under the umbrella term ‘biological drugs’ they have distinct and unique characteristics that warranted their classification as a distinct type of drugs; these specialized medicinal products are therefore referred to as advanced therapy medicinal products (ATMP). The respective piece of legislation, the so-called ATMP Regulation (Regulation (EC) No 1394/2007) defines these medicinal products as follows:

(a) ‘Advanced therapy medicinal product’ means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined in Part IV of Annex I to Directive 2001/83/EC,
— a tissue engineered product as defined in point (b).

Each drug type will be defined in more detailed in the following paragraphs. In addition, a fourth category of ATMPs will be introduced, the so-called ‘combined ATMPs’.
a. Gene therapy (GT) medicinal products

Gene therapy (GT) medicinal products were already described in Part IV of Annex I of the Community Code (Directive 2001/83/EC):

*Gene therapy medicinal product* means a biological medicinal product which has the following characteristics:

1. 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;
2. 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.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

Gene therapy medicinal products (GTMP) include a range of different products such viral and non-viral vectors, which includes plasmid DNA, as well as genetically modified viruses and cells.

b. Somatic cell therapy (SCT) medicinal products

The same Directive also includes a definition for somatic cell therapy (SCT) medicinal products:

*Somatic cell therapy medicinal product* means a biological medicinal product which has the following characteristics:

1. 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 of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;
2. 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.

For the purposes of point (a), the manipulations listed in Annex I to Regulation (EC) No 1394/2007, in particular, shall not be considered as substantial manipulations.

A critical element of this definition of SCTs is the fact that the cells or tissues must have been manipulated in a certain manner in order to achieve their intended mode of action in humans. For further clarification, Annex I of the Regulation lists a number of procedures which alone are not considered as manipulation of the original cells and tissues in the meaning of the ATMP Regulation; these include cutting, grinding, centrifugation, sterilization, irradiation, cell separation, concentration or purification, lyophilization, or cryopreservation.
c. Tissue-engineered products (TEP)

While GT and SCT medicinal products had already been defined in previous legislation, the ATMP Regulation (Regulation (EC) No 1394/2007) for the first time introduced a legal definition of tissue-engineered products (TEP):

**Article 2, 1(b):**

(b) ‘Tissue engineered product’ means a product that:

- contains or consists of engineered cells or tissues, and
- 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.

A tissue engineered product may contain cells or tissues of human or animal origin, or both. The cells or tissues may be viable or non-viable. It may also contain additional substances, such as cellular products, bio-molecules, biomaterials, chemical substances, scaffolds or matrices.

Products containing or consisting exclusively of non-viable human or animal cells and/or tissues, which do not contain any viable cells or tissues and which do not act principally by pharmacological, immunological or metabolic action, shall be excluded from this definition.

While TEPs and SCTs may consist of similar components (e.g. cells, matrices and scaffolds etc.), a key difference between the two types of cell-based medicinal products (CBMP) therefore is their different intended use – in the case of SCTs it is the treatment, prevention or diagnosis of a disease through the cells’ or tissues’ pharmacological, immunological or metabolic action. With TEPs, on the other hand, the cells or tissue are being administered in order to regenerate, repair or replace human tissue (e.g. via tissue transplantation).

Cells or tissues may be either sourced from the patient himself (autologous) or from another human being (allogeneic). ATMPs that contain both allogeneic and autologous cells or tissues are considered to be for allogeneic use (Article 2 (3) of the ATMP Regulation).

In cases where a medicinal product falls both within the definition of a TEP and a SCT, the product will be considered a TEP by definition (Article 2 (4) of the ATMP Regulation).

d. Combined ATMPs

ATMPs containing cells or tissue may also include medical device components as an integral part of the medicinal product (e.g. matrices, scaffolding etc.). In these cases the requirements of the Medical Device Directive (MDD) (Directive 93/42/EEC) and the Directive on Implantable Medical Devices (Directive 90/385/EEC), as applicable, need also be considered during the development, licensing and commercialization of the combination product.

**ATMP Regulation, Article 2 Definitions**

(d) ‘Combined advanced therapy medicinal product’ means an advanced therapy medicinal product that fulfils the following conditions:
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, and
- its cellular or tissue part must contain viable cells or tissues,

or

- 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.

Of note, combined ATMPs always fall under the ATMP Regulation, regardless of the role of the device component. In addition, the medical device directives may be applicable to combined ATMPs, depending on the nature of the device component. The final approved product may include the medical device at the core of its action; therefore, any changes in either the medical device or biological component need to be reevaluated by the regulatory bodies. Consequently, the full development of the medical device component is crucial in early clinical stages.

4. Borderline considerations

Borderline cases could appear as a consequence of the product definitions mentioned above where the classifications of drugs, ATMPs and medical devices overlap and a clear delineation between product types is not immediately obvious. However, since the regulatory requirements for the different types of healthcare products differ, the correct classification of a product is critical and should be determined at an early stage of development.

For a classification decision the concept of a product’s intended use as well as the notions of pharmacological action and physical means are important criteria. This means, a decision will depend on whether a product is actually being “presented as having properties for treating or preventing disease” (i.e. the claims that are made for the product (Article 1 of Directive 2001/83/EC, definition of a ’medicinal product’) and whether the product is intended to be administered with a view to achieving a medicinal purpose.

As mentioned above, in the case of an ATMP-device combination, the product always falls under the ATMP Regulation, and the applicable device regulations need to be adhered to in addition. Furthermore, there can be borderline cases with cosmetics, transplants or other product types. In these cases, manufacturers can apply for an optional scientific recommendation procedure (see 4. Scientific recommendation on classification of ATMPs (“ATMP classification”)).
Section II. – Regulation of ATMPs in Europe

1. Introduction of Regulation (EC) 1394/2007

The advances in science and research have yielded a new class of innovative and complex biological medicinal products that are based on manipulated genes, cells or tissues, so-called advance therapy medicinal products (ATMP). While these products have the potential to address unmet medical needs in the treatment of disease as well as the repair of tissue or organ defects, these novel health technologies also involve specific risks (e.g. immunogenicity, viral safety, tumorigenicity etc.) that need to be accounted for in an appropriate regulatory framework.

Historically, this regulatory context for cell or gene based therapies was very heterogeneous across EU Member States and resulted in divergent national procedures for classification and authorization. Regulation for these types of products ranged from no (specific) regulation at all, to being regulated as medicinal products or as devices. In order to bridge this regulatory gap, to create a level playing field for ATMP manufacturers and to ensure the free movement of medicinal products across the EU, the European Commission identified the need to harmonize the regulatory landscape for this innovative class of medicinal products (Commission staff working document 2005).

On 30 October 2007 the European Council formally adopted a lex specialis in the form of the regulation on advanced therapy medicinal products (Regulation (EC) No 1394/2007),$^2$ which applies in the European Union since 30 December 2008. The so-called ATMP Regulation lays down specific rules for the authorization, supervision and pharmacovigilance of ATMPs and set up the Committee for Advanced Therapies (CAT). It regulates advanced therapies that are prepared industrially or manufactured by a method involving an industrial process and that are intended to be placed on the EU single market (i.e. those products that fall within the scope of Directive 2001/83/EC).

The ATMP Regulations amends the two important legislative acts for pharmaceuticals – Directive 2001/83/EC and Regulation (EC) 726/2004) –, i.e. the provisions of the ATMP Regulation are now also reflected in those acts.

The regulation was designed to facilitate the access of advanced therapies to the EU market, to ensure their free movement within Europe as well as to foster the competitiveness of European companies in the field. At the same time, the regulation should ensure a high level of human health protection.

The main elements of the ATMP Regulation are:

- A centralised marketing authorisation procedure for ATMPs, to benefit from the pooling of expertise at European level and direct access to the EU market.
- A new and multidisciplinary expert Committee (Committee for Advanced Therapies, CAT), within the European Medicines Agency (EMA), to assess advanced therapy products and to follow scientific developments in the field.
- Technical requirements adapted to the particular characteristics of these products.
- Special incentives for small and medium-sized enterprises (SME)

$^2$ Published in the Official Journal on 10/11/2007
The legislation foresaw a transitional phase for ATMPs that were already legally on the market in the EU. The transition period ended on 30 December 2011 for GT and SCT products and on 30 December 2012 for TEPs, respectively. From these time points forward, the advanced therapies had to comply with the requirements of the ATMP Regulation.

According to recital 7, the ATMP Regulation does not affect decisions of individual Member States about the use of embryonic stem cells or animal cells. The sale, supply or use of medicinal products consisting of or derived from these types of cells may still be covered by national legislation.

2. Committee for Advanced Therapies (CAT)

To ensure that the best available expertise is applied to the evaluation of these complex and novel products, the ATMP Regulation called for the establishment of a dedicated scientific committee within the EMA, the Committee on Advanced Therapies (CAT) (Chapter 7 of the ATMP Regulation).

The CAT is a multidisciplinary group composed of around 37 members with a wide area of expertise (including bordering disciplines like medical devices):

- 5 members (plus alternates) of the Committee for Medicinal Products for Human Use (CHMP);
- 1 member (plus alternate) from each EU Member State that is not yet represented by the 5 CHMP members;
- 2 members (plus alternates) representing clinicians appointed by the Commission;
- 2 members (plus alternates) representing patients’ associations appointed by the Commission.

Importantly, all CAT members are chosen for their specific scientific qualifications and expertise in the areas relevant to advanced therapies including medical devices, tissue engineering, gene and cell therapy, biotechnology, surgery, pharmacovigilance, risk management and ethics. Furthermore, additional experts can be consulted whenever deemed necessary by the committee. The CAT members are appointed for a renewable term of 3 years and elect a chairman from among the committee for the same period.

The composition of the CAT, including contact details and CVs of each expert, are published on the EMA website under the “Committees” section. This site also includes the meeting dates of the CAT as well as agendas, minutes and reports of committee meetings.

The Committee is responsible for the assessment of the quality, safety and efficacy of ATMPs. As a committee of the EMA, the CAT applies the general provisions of the Community procedures for the authorization, supervision and pharmacovigilance of medicinal products (Regulation (EC) No 726/2004). During the marketing authorization (MA) procedures, they carefully assess the application dossier and all data provided on the new medicinal product against the criteria set out in Community Code (Directive 2001/83/EC). The outcome of the CAT review is a draft opinion on whether the application for marketing authorization (MAA) for the advanced therapy medicinal product should be
recommends for approval\(^3\). The CHMP is then responsible for issuing the final recommendation on the MAA to the European Commission, which ultimately grants the marketing authorization.

In addition to its close collaboration with the CHMP, the CAT also works closely with other specialized functions within the EMA, such as the Committee for Orphan Medicinal Products (COMP), the Pharmacovigilance Risk Assessment Committee (PRAC) the Scientific Advice Working Party (SAWP) as well as other working parties.

Details about the Committee’s composition, operating principles and assessment procedures are outlined in the CAT Rules of Procedure (2014).

3. Incentives of the ATMP Regulation

The ATMP Regulation has introduced a number of incentives to manufacturers of advanced therapies, particularly small and medium-sized enterprises (SME) (Chapter 6 of Regulation (EC) No 1394/2007). These incentives include:

- Scientific advice on the design and conduct of Pharmacovigilance and risk management systems;
- A fee reduction of 90% for SMEs and 65% for other applicants on any scientific advice given with respect to ATMPs;
- Scientific recommendation on advanced therapy classification (see section 4. Scientific recommendation on classification of ATMPs (“ATMP classification”));
- Certification of quality and non-clinical data (see section 5. Certification of quality and non-clinical data);
- Reduction of the fees for marketing authorization (50%) for hospitals and SMEs if a public health interest in the ATMP can be proven; furthermore, the 50% fee reduction is also granted for post-authorization activities in the first year following the granting of the product’s marketing authorization.

A few of these incentive programs will be described in more detail in the following sections. In addition, ATMP manufacturers should consider other programs available for medicinal products in general, such as the orphan drug designation procedure, scientific advice or protocol assistance or the registration as a small and medium-size enterprise (SME) with the SME Office at the EMA (see Appendix 2 and Appendix 3).

4. Scientific recommendation on classification of ATMPs (“ATMP classification”)

In the past there had been cases where Member States came to divergent conclusions about whether an innovative biological product should be classified as medicinal product, medical device or ATMP. Such disparity would result in the same product falling under different regulatory frameworks in different countries. This posed a great uncertainty to ATMP manufacturers with regard to a product’s

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\(^3\) Of note, in the European Union, the EMA and its committees are responsible for the scientific assessment of MAAs; upon completion of their review, it issues an opinion to the European Commission, the body that is responsible for the granting of a marketing authorization.
market potential, hindered the product’s free movement across EU Member States and was undesirable from a public health perspective.

The ATMP Regulation (Article 17) has therefore introduced an optional procedure that allows manufacturers of products based on genes, cells or tissues to seek a scientific recommendation from the CAT on whether their product can be classified as an ATMP. Since the regulatory framework differs significantly between the various healthcare products (medicinal products, medical devices, ATMPs etc.), it is critical for developers of new therapies to have clarity about their products classification at an early stage of development. In addition, the ATMP classification allows identifying the applicable regulatory and scientific guidelines for a given drug’s development path as well as all applicable procedures and incentives. Furthermore, the ATMP classification offers the opportunity to initiate an early dialogue with regulators and can help facilitate the clinical trial authorization (CTA) process on Member State level.

The ATMP classification is a 60 days procedure at the end of which the CAT – in close collaboration with the European Commission (EC) - offers a non-binding classification recommendation for a defined product. The recommendation can be sought at an early stage of development, i.e. non-clinical or even clinical data need not yet be available. The outcome of the CAT’s assessment of the ATMP classification is being published on the EMA website as “summaries of scientific recommendations on classification of advanced-therapy medicinal products” (www.ema.europa.eu > Human regulatory > Advanced therapies > ATMP classification > Summaries). Should new scientific information become available subsequent to the conclusion of classification procedure, the applicant has the opportunity to request a follow-up assessment.

Of note, the ATMP classification is free of charge for applicants and the advice is non-binding.

The details of the ATMP classification procedure, including the type and amount of information to be submitted by the applicant, are described in a CAT guidance document (Reflection Paper on ATMP Classification 2010). The paper also includes a non-exhaustive list of scientific criteria that the CAT applies for its classification recommendations, such as

- Claimed mode of action, i.e. is the product intended to treat, prevent or diagnose a disease? Does it exert its activity via pharmacological, immunological or metabolic action, or is it intended to regenerate, repair and replace human cells or tissues?
- Criteria for gene therapy medicinal products (GTMP):
  - Are both criteria of the GT definition fulfilled (see section 3.a.)?
- Criteria for somatic cell therapy medicinal products (sCTMP) and tissue-engineered products (TEP)
- Criteria for combined ATMPs
- Evolving and borderline areas

The Reflection Paper includes references to real-case examples of the CAT’s previous assessments, which help to illustrate the principles underlying the ATMP classification. Furthermore, decision trees for GTMPs as well as SCTMP and TEPs, respectively, help applicants to classify their products.

After 5 years of experience with the classification of ATMPs, in June 2014, the EMA published a draft Reflection Paper on classification of advanced therapy medicinal products for public consultation (Reflection Paper on ATMP Classification 2014). This paper reflects the current thinking of the CAT
on aspects of substantial manipulation and non-homologous use, amongst other updates. Following the public consultation period, a revision of the classification guideline will be drafted, taking into consideration any stakeholder comments received.

5. Certification of quality and non-clinical data

a. Background

As a special incentive to SMEs developing advanced therapies, the ATMP Regulation (Article 18) includes a provision that these organizations can submit the available quality and non-clinical data for their advanced therapy product to the CAT for scientific evaluation and certification. This evaluation of quality and non-clinical data essentially applies the same scientific standards and technical requirements as during the assessment of marketing authorization (MAA), just at an earlier stage of development. This new assessment instrument was intended to help SMEs to attract capital and to facilitate the transfer of their early research to entities capable to advance the ATMP’s development through the clinical stage and marketing authorization (EC Report COM (2014) 188 final). In principle, SME applicants can submit applications for certification at any stage of development of their ATMP; however, to allow for a meaningful assessment of the data by the CAT, a minimum level of manufacturing and testing data should be available. The certification application is expected to include a clear description of the active substance, finished product as well as its intended clinical use / indication and the proposed route of administration.

While the certification system is a stand-alone evaluation procedure that is procedurally independent from other regulatory activities, it aims to facilitate the preparation of clinical trial authorization (CTA) or MAA dossiers for ATMPs. Furthermore, the certification procedure allows the SME applicant to engage in an early dialogue with the regulators (i.e. the ATMP experts at the CAT). The documented assessment of the quality and non-clinical data may also be of value for out-licensing activities or when trying to raise funds.

An SME can apply for certification of quality data only or of both, quality and non-clinical data.

The details of the certification procedure are described in the CAT Procedural advice on the certification of quality and non-clinical data for small and medium sized enterprises developing advanced therapy medicinal products (Procedural advice on certification (EMA/CAT/418458/2008/corr.)). The guidance describes the procedural steps and timelines of the certification process, from the submission of the application to EMA to the data evaluation and ultimately the issuing of the certificate. In addition, the structure and format of the application are indicated.

It is worth mentioning that the ATMP certification procedure only assesses the already available quality and non-clinical data, as applicable. Advice on the further development and any future studies does not fall within the scope of the certification; rather, feedback on prospective development plans should be sought via the regular scientific advice procedure (see Appendix 1, 3. Scientific advice procedures).

Since only SMEs are eligible for the ATMP certification procedure, the applicant needs to hold a valid SME status when submitting an application for the certification procedure. For further information on the procedure or in case of any questions, applicants can contact the SME Office at the EMA for 18/70
further guidance. In case of doubts whether the product under development can actually classified as an ATMP, companies may seek confirmation from the CAT (see section 4. Scientific recommendation on classification of ATMPs (“ATMP classification”)).

b. Data package for certification
The manufacturing and non-clinical files submitted for certification already represents a subset of the data ultimately required in Module 3 (Quality) and Module 4 (Non-clinical) of a MAA. For that reason, all data should be submitted in the format of the Common Technical Document (CTD) according to the Notice to Applicants, Volume 2B. The amount of data to be submitted should represent the products stage of development. In cases where the ATMP is already being tested in clinical trials, appropriate information should be provided in Module 2 (section 2.2 Introduction) as supportive information; while it is not part of the certification procedure, the initial clinical data will be helpful as it reflects the stage of product development and the intended use of the product.

To aid in the preparation of the appropriate quality and non-clinical documentation, the CAT has issued a Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (2010). The guideline includes a tabular overview of the content of Module 3 (Quality) with specific guidance for ATMPs in general and cell-based or gene therapy medicinal products in particulars. Furthermore, the minimum requirements for non-clinical data as appropriate for the stage of development are given. The expectations for Module 4 (Non-clinical reports) are as follows:

1. **Proof of concept/principle** (primary pharmacodynamics (PD)): results of *in vitro* studies and at least one study in a relevant *in vivo* animal model(s) reflecting the intended clinical use, if feasible.
2. **Biodistribution** (pharmacokinetics (PK)): PK data is generally considered critical to support the PD and safety of the ATMP. The data is usually derived from dedicated PK studies or as part of toxicity studies.
3. **Safety** (toxicology / safety pharmacology): the application for certification of non-clinical data should include at least one safety study. They should be conducted in accordance with GLP principles and standards (even though they need not necessarily be full GLP studies).

The guideline clearly specifies that only final reports of the above mentioned studies will be accepted. The submission of interim data from ongoing studies is discouraged. The final reports should be presented under the appropriate headings of the CTD Module 4.

c. Certification procedure
According to the legislation, the certification procedure is only open to SMEs that are developing ATMPs and are established within the Community.

The actual certification procedure at the EMA includes an up to 95 days assessment process; in addition, approximately 70 days need to be calculated from submission of the letter of intent (LOI) until the clock-start of the CAT scientific assessment. The sequence of activities is summarized in Table 1. Further details on each procedural step are given in the CAT Procedural advice on certification (EMA/CAT/418458/2008/corr).
Of note, as most procedures at the EMA, the certification procedure follows a *standard timetable*; i.e. applications made by a certain submission deadline will be assessed according to pre-determined fixed timelines. These deadlines and subsequent dates of procedural milestones are published on the EMA website under *(www.ema.europa.eu > Human regulatory > Advanced therapies > Certification procedure for SMEs > Submission deadlines)*.

**Table 1. Activities and timelines for the Certification procedure**

<table>
<thead>
<tr>
<th>Timeline</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day -70</strong></td>
<td><strong>Pre-submission request form</strong> (Intent to submit a certification procedure) sent by Applicant (at the latest 10 days before the CAT meeting → meeting dates available on the EMA website). → General template letter available on EMA website (“pre-submission request form”) → Request letter to be submitted to <a href="mailto:PA-BUS@ema.europa.eu">PA-BUS@ema.europa.eu</a> EMA checks if SME/ATMP criteria are fulfilled.</td>
</tr>
<tr>
<td><strong>Day -60</strong></td>
<td>Appointment of CAT Coordinator, CAT peer reviewers and EMA Coordinator.</td>
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<tr>
<td><strong>Day -50</strong></td>
<td>Submission of draft certification application to EMA and Coordinators for pre-validation.</td>
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<tr>
<td><strong>Day -40 to -20</strong></td>
<td><strong>Pre-submission meeting</strong> (teleconference) with EMA Coordinator/(CAT Coordinator).</td>
</tr>
<tr>
<td><strong>Day -10</strong></td>
<td>Submission of final application to EMA, for validation. → The documentation to be included in the application is detailed in the CAT’s procedural advice document</td>
</tr>
<tr>
<td><strong>Day -5</strong></td>
<td>Submission of final application to CAT Coordinator, CAT peer reviewers and CAT members.</td>
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<tr>
<td><strong>Day 0</strong></td>
<td><strong>Clock start (at official CAT start date)</strong> → assessment timetables published on EMA website</td>
</tr>
<tr>
<td><strong>Day 40</strong></td>
<td>Circulation of Coordinator’s certification evaluation report to the CAT. Subsequent transmission of this report, by the EMA, to the Applicant.</td>
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<tr>
<td><strong>Day 40-60</strong></td>
<td>Consultation of relevant Working Parties, as appropriate.</td>
</tr>
<tr>
<td><strong>Day 50</strong></td>
<td>Peer review comments from CAT Peer Reviewers. Comments by other CAT members.</td>
</tr>
<tr>
<td><strong>Day 55</strong></td>
<td>Circulation of Coordinator’s consolidated certification evaluation report including relevant CAT members’ comments.</td>
</tr>
<tr>
<td><strong>Day 60</strong></td>
<td>CAT discussion/recommendation / (possible opinion). Adoption of request for supplementary information (RSI), if necessary (clock stop)* CAT adoption of <strong>site visit</strong>, if necessary (clock stop)** → Site visits of premises where the ATMP is being manufactured or non-clinical testing being conducted may be requested if considered necessary to complete the certification evaluation. CAT decision to consult a relevant NB, if necessary (clock-stop)** → in case of combined ATMPs</td>
</tr>
</tbody>
</table>
| **Day 60** | **Clock-stop (if necessary)** */**
### Timeline

| Day 61 | Applicant’s submission of responses to RSI  
|        | Restart of the clock. Written/Oral*** explanation. |
| Day 75 | Circulation of updated consolidated Coordinators’ certification evaluation report to the CAT. Subsequent transmission of this report, by the EMA, to the Applicant. |
| Day 85 | Comments from CAT members. |
| Day 90 | CAT adoption of opinion including the following document: Certification evaluation report including a list of issues. |
| Day 95 | EMA issues the certificate or an advisory letter and forwards the adopted documents to the Applicant. |

**A response timetable may be arranged as necessary (30-60 days). The clock will restart at the next or second next CAT meeting (this will be Day 61).**

**A response timetable may be arranged as necessary (until the site visit report/ NB opinion is made available to CAT and EMA).**

**The responses to the request of supplementary information should be provided at least 20 days before the scheduled oral explanation. The CAT Coordinator prepares and circulates the updated consolidated Coordinators’ certification evaluation report 10 days before the oral explanation. The Applicant provides the presentation 7 days before the CAT meeting to EMA, CAT Coordinators and CAT members.**

[From: Procedural advice on certification (EMA/CAT/418458/2008/corr.)]

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### d. Outcome & follow-up certification

The outcome of the procedure is an EMA certificate based on the CAT opinion as well as a detailed **certification evaluation report**. The report will comment on the quality and acceptability of the submitted data in terms of their regulatory compliance and scientific robustness as needed for a marketing authorization (as defined in Directive 2001/83/EC). The report will indicate the reasons for the CAT’s conclusions as well as a list of issues the applicant is advised to address in future regulatory filings.

- Positive certification evaluation: EMA issues a **certificate**.
- Negative certification evaluation: EMA issues an **advisory letter**.

Importantly, the certificate is not legally binding with regard to future regulatory procedures (such as an MAA filing) and the validity of the certificate is linked to the time point/stage of development when the certification was issued.

In case significant new quality or non-clinical data on a previously certified product becomes available, a **follow-up certification** can be applied for. Of note, a justification of the significance of the new information as well as the differences compared to the initial certification procedure need to be provided by the applicant.

An update to the certification procedure is foreseen once necessitated by the growing experience of the CAT with the procedure.

In 2014, the **basic fee** for the certification procedure was €41,700.- for evaluation of quality data only and € 62,700.- for the evaluation of quality and non-clinical data. Similar as for scientific advice procedures, the EMA grants a fee reduction of 90% to certification requests by SMEs (Explanatory note on fees payable (2014)). Of note, the EMA’s fees are being adjusted as of 1 April each year and the current fees should be looked up on the agency’s website.
6. Role of EMA and NBs for combined ATMPs

As other biotechnology-derived medicinal products, ATMPs are now being authorized for marketing through the centralized procedure, i.e., a single assessment procedure may lead to a marketing authorization that is valid in all EU Member States. The procedure for the scientific evaluation of these medicines by the European Medicines Agency (EMA) is governed by Regulation (EC) 726/2004. It introduced a single assessment procedure for the evaluation of an innovative product’s quality, safety and efficacy which is now also mandatory for ATMPs.

Combined ATMPs, by definition, incorporate a medical device component as an integral part. Therefore, it must also comply with the essential requirements of medical devices or active implantable medical devices and assessed by a Notified Body (NB), as appropriate (Directive 93/42/EEC and Directive 90/385/EEC, respectively). The EMA/CAT and Notified Bodies Collaboration Group has been set up to facilitate the implementation of the requirements of the ATMP Regulation for combined ATMPs. The mandate, objectives and rules of procedure of EMA/CAT-NB as well as their work plan is published on the EMA website under www.ema.europa.eu > Committees > Working parties and other groups > CAT > EMA/CAT-NB.

The coordination between CAT/EMA and the responsible NB during an MAA assessment procedure is described in a guidance document (Procedural advice on evaluation of combined ATMPs) and summarized in Section IV 3. Combined ATMPs and Notified Bodies.

7. Hospital exemption

The ATMP Regulation, in line with the general scope of Directive 2001/83/EC, applies to advanced therapy medicinal products manufactured by industrial methods and intended to be placed on the market in EU Member States. Under the so-called hospital exemption, certain ATMPs are excluded from its provisions (Article 3(7) of Directive 2001/83/EC 2001), namely if they are

- Prepared on a non-routine basis according to specific quality standards,
- Used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner,
- In order to comply with an individual medical prescription for a custom-made product for an individual patient.

Custom-made advanced therapy medicinal products falling under the above exemptions do not need to apply for a marketing authorization, but can rather be authorized for use by the concerned Member State if they apply with national requirements for quality, traceability and Pharmacovigilance that are equivalent to those for ATMPs with a centralized marketing authorization. This non-routine application of ATMPs was intended to facilitate the research and development of advanced therapies by academic groups, hospitals or not-for-profit organizations.

In countries where the requirements for hospital exemptions have already been transposed into national law, the exact domestic implementation varies across Member States, sometimes even resulting in divergent rules (Cuende, et al. 2014). These national differences mainly arise because key terms such as “industrial process”, “custom made product” or “non-routine basis” have not been
explicitly defined in the Directive/legislation. As outlined in a working document of the European Commission (EC) (Commission staff working document 2005), the meaning of “industrial process” was intended to cover, inter alia:

- any ‘mass production’ of advanced therapy products for allogeneic use (batch production, ‘on the shelf’ products etc.);
- any advanced therapy product for autologous use which, although being patient specific by definition, is manufactured in accordance with a standardised and industrial process.

However, the absence of a binding EU-wide definition unsurprisingly led to different and sometimes conflicting national interpretations. Critically, already the question when the HE applies to an advance therapy actually varies considerably from one country to the next. A few Member States, for instance, have set specific numbers or criteria to define “non-routine basis” (e.g. the Netherlands (Procedure for hospital exemption 2011), Germany (German Drug Law)), while other national provisions do not specify any quantities (Cuende, et al. 2014). Also the entity required to hold the HE license differs; while in most Member States it is the ATMP manufacturer who is granted the exemption, in Spain and Portugal the obligation to request the HE and submit the appropriate dossier falls to the hospitals. Furthermore, the need for quality, safety and/or efficacy data requirements for an HE application vary markedly. Spain, for example, expects quality, non-clinical as well as clinical data to be available for an HE (Real Decreto 477/2014), while in Finland small-scale clinical use may be carried out while non-clinical studies in support of a future clinical trial are still ongoing (Cuende, et al. 2014). The Netherlands considers HEs similarly to compassionate use, i.e. as an alternative for patients that are not eligible for clinical trials. Portugal, on the other hand, has not implemented any provisions as to when HE applies (Portaria n.° 138/2014 de 7 de julho). Divergent requirements are also seen in the need for a qualified person for manufacturing.

In France ATMPs falling under the hospital exemption are considered “preparations”. Establishments that want to prepare, preserve, distribute and transfer ATMPs under the hospital exemption rules need to be authorized by the French competent authority (Agence nationale de sécurité des médicaments et des produits de santé, ANSM), a procedure that includes an opinion of the Biomedicine Agency (l’Agence de Biomédecine (ABM); www.agence-biomedecine.fr) (Mahalatchimy 2012). Requirements for clinical trials under the HE are the same as for other medicinal products.

And finally, also the validity of a HE varies considerably – from product-specific licenses for 10 batches or 1 year (the Netherlands) and one year plus option for renewal (Portugal) to authorizations for initially 3 and subsequently 5 years (Spain) or no limitations on the licensing period (Germany) (Cuende, et al. 2014).

Therefore, the specific requirements in each country need to be clarified individually with the competent authority concerned. Importantly, ATMPs falling under the hospital exemption have to be prepared and used within the same Member State, i.e. they cannot be exported to another country. A notable exception are the UK regulations, where the manufacturing and supply of unlicensed ATMPs may also be granted under the “specials” scheme according to Article 5(1) of Directive 2001/83/EC, allows import and export activities for the concerned ATMPs.
8. Experience with ATMP Regulation to date

As foreseen in the ATMP Regulation (Article 25), the European Commission issued a general report to review the scope and application of the regulation and to assess the impact of technological progress. In order to prepare for this report, the Commission had launched a public consultation of stakeholders asking them for their opinions on the ATMP Regulation in general as well as their specific experience with certain provisions (e.g. hospital exemption, incentives etc.). The final Commission report, which covers the experience with the application of the ATMP Regulation between 1 January 2009 and 30 June 2013, was published on in March 2014 (EC Report COM (2014) 188 final).

The report reemphasizes the objectives of the ATMP Regulation, such the generation of a common regulatory framework for ATMPs across the EU and the protection of patients from scientifically unsound treatments.

By 30 June 2013 only 4 ATMPs had received a marketing authorization according to the new legal requirements: **ChondroCelect** (a TEP), **Glybera** (GTMP), **MACI** (combined ATMP) and **Provenge** (SCTMP) (see also Section VI – Approved ATMPs in the EU – Examples). A 5th ATMP (**Holoclart**) has been recommended for approval in the EU in December 2014.

The establishment of the CAT as a specialized scientific body dedicated to ATMPs was a major milestone. The set-up of a collaboration group between the committee and the notified bodies (NB) is welcomed. The number of ATMP classifications and scientific advice related to the development of advanced therapies is highlighted.

By 30 June 2013, the CAT had issued 81 ATMP classification recommendations, of which approx. 65% were requested by SMEs or not-for-profit organizations. At the same time, the EMA provided scientific advice in almost 100 cases concerning approx. 65 different products. In contrast, during the same period only 3 SMEs had requested a certification of their quality and non-clinical data.

- Availability of ATMPs across the EU

By 30 June 2013, only ten MAAs for ATMPs had been received by the EMA, with only 4 being granted marketing authorization via the centralized procedure. And while it has proven difficult to obtain precise numbers of advanced therapies legally on the market in the EU prior to the implementation of the regulation, it can be assumed that a significant number of ATMP developers with products previously on the market did not apply for an MA in accordance with the new regulation. This is supported by a correspondingly high number of derogations from the requirements to seek a MA prior to marketing of a new ATMP (such as hospital exemptions).

The too broad application of the hospital exemption provisions is raising concerns that it puts marketing authorization holders (MAH) of approved ATMPs at a competitive disadvantage, e.g. due to higher costs associated with stricter data requirements and post-marketing obligations. The high number of hospital exemptions may also reduce the number of clinical trials and patients treated with ATMPs and thus diminish the evidence of safety and efficacy ultimately available for advanced therapies. Ultimately, the innovative treatment approaches ATMPs offer would not be available to all patients within the Community. Therefore, it is recognized that the early access to new therapies for patients without any treatment options needs to be carefully balanced with the need to adequately demonstrate an ATMP’s quality, safety and efficacy prior its broad administration to patients. The EC report therefore recognizes the need to further clarify the conditions under which the hospital
exemption should apply, as well as to which extent the data obtained under these circumstances could be used within a later MAA.

- **Classification procedures**

The classification procedure was introduced to provide clarity to applicants/manufacturers about the correct classification and thus correct regulatory framework that applies to their specific innovative biological drug candidate (e.g. medicinal product, medical devices, tissue or cells). Certainty on a product’s correct classification is essential in order to devise and pursue the appropriate development path.

According to the EC report, the CAT had issued 81 classification recommendations for a total of 87 requests received. Almost half of these requests were submitted by SMEs, approx. 15% by non-profit organizations and only 5% by large pharmaceutical companies.

These classification recommendations mean a single viewpoint on the concerned products throughout the EU and provide the intended certainty to the manufacturers. However, the report also points out certain shortcomings of the procedure. For instance, due to its non-binding nature the developer may disregard the CAT’s advice and choose not to develop the safety and efficacy data or follow the quality or pharmacovigilance requirements for medicinal products. Also, at present NCAs do not have the opportunity to seek the CAT’s view when they are confronted with the question of an innovative product’s correct classification.

- **Certification procedure**

During the period covered by the EC report, only three certification requests have been received, which is considered disappointing. One reason for this low interest in a tool that was intended as an incentive to ATMP developers might be its restriction to SMEs. Expanding the group of eligible applicants might therefore improve the practical value of the certification procedure, as might be the option to also include available clinical data into the assessment.

In 2013, EMA published the outcome of a survey on ATMP certification for SMEs (EMA survey on ATMP certification (EMA/66222/2012)). The survey was intended to solicit feedback from SMEs on why the certification procedures was not more widely used, as well as suggestions on how the procedure could be improved. In summary, the respondents saw the main advantages of the procedure in clarifying the regulatory requirements, facilitating the preparation and simplifying the filing and evaluation of MAA. In addition, companies saw some value in the certification procedure for the funding and/or in/out licensing of their products. The absence of a direct link between certification and marketing authorization was indicated as a major shortcoming of the procedure. Also, there seemed to be confusion about the difference between a scientific advice and the certification procedure.

- **Marketing authorization procedure**

The centralized marketing authorization procedure is already rather complex for conventional drugs; however, for ATMPs it is further complicated due to the involvement of an additional scientific committee (CAT) and the integration/coordination of additional outside stakeholders such as notified bodies (NB). This is further compounded by the fact that developers of ATMPs are typically SMEs or not-for-profit organizations with limited experience with these types of regulatory interactions.

The EC report identified further room for improvement, especially with regard to streamlining the assessment procedure of ATMPs as well as clearer allocation of responsibilities within the EMA.
• Fee incentives

The 50% reductions in fees for MAA or post-marketing obligations that were only granted for a limited period of time and no longer apply. The EC report points out that the often significant fees associated with post-marketing activities can be prohibitively high for SMEs, especially when protracted national reimbursement decisions delay the generation of appropriate revenue from the new ATMP.
Section III. – Pre-marketing authorization for ATMPs

As any medicinal products, in order to obtain marketing authorization manufacturers of ATMPs need to be able to demonstrate that their product can be consistently manufactured in accordance with predefined quality standards and establish that it is safe and efficacious in the intended target population (Directive 2001/83/EC). However, given the unique and complex nature of this product class, the ATMP Regulation included provisions for the Commission to develop specific requirements for advanced therapies with regard to the content of marketing authorization applications (MAA), Good Manufacturing Practices (GMP), Good Clinical Practices (GCP) as well as the traceability of ATMPs. In some areas these requirements have already been adopted (MAA content, GMP for ATMPs) while the specific guidance on GCP and traceability are currently still pending (EC Report COM (2014) 188 final). This section will summarize the main adaptations of the regulatory framework for ATMPs.

Of note, cell-based medicinal products (CBMP) are very heterogeneous and differ, for instances, in the origin and type of cells, their stage of differentiation and in the inherent complexity of the advanced therapy product. In addition, they may be combined with a device component (combined ATMP). Therefore, drug development considerations need to be taken on a case-by-case basis and strategies need to be justified for each individual product, applying a risk-based development approach. Some general considerations for the development of CBMPs are summarized in the multidisciplinary Guideline on Human Cell-based Medicinal Products (2008). The methodology for ATMPs in general is outlined in the CAT’s Guideline on risk-based approach for ATMPs (2011).

1. Risk-based approach

The class of ATMPs comprises a heterogeneous group of products that differ widely also in the risks associated with their handling and administration. The standard data requirements for an MAA to establish a drug’s quality, safety and efficacy may not be fully adequate for ATMPs. Therefore, a flexible approach to the clinical use of ATMPs has been introduced that is intended to evaluate and address the risk profile of each individual product (Directive 2009/120/EC amending Directive 2001/83/EC). The practical implementation of these legal requirements is outlined in the CAT’s Guideline on the risk-based approach according to Annex I, Part IV of Directive 2001/83/EC applied to Advance therapy medicinal products (Guideline on risk-based approach for ATMPs).

The risk-based approach can be used to determine the amount and type of quality, non-clinical and clinical data to be included in the MAA. Applying these risk-based principles is optional; however, if chosen the approach should be applied from the beginning of the product development and updated regularly as the knowledge about the product increases.

The guideline outlines the general methodology to be used for the identification and evaluation of product-specific risks (e.g. tumorigenicity) and their associated risk factors. Based on the resulting risk profile the manufacturer may justify the extent of data included in the MAA dossier.

**Risks** are defined as a “potential unfavourable effect that can be attributed to the clinical use of ATMP and is of concern to the patient and/or to other populations (e.g. caregivers and offspring)”. Examples of risks associated with the clinical use of ATMPs include immunogenicity, disease
transmission or inadvertent germ line transduction, as well as toxicities due to degradation/leaching of toxic compounds from structural components or deregulated therapeutic gene expression. A risk factor is defined as a “qualitative or quantitative characteristic that contributes to a specific risk following handling and/or administration of an ATMP”. Examples of risk factors are the origin of cells or tissues (autologous vs. allogeneic vs. xenogeneic), the ability of cells to proliferate and/or differentiate, the level of cell manipulation, the level of integration of nucleic acids sequences or genes into the genome, the mode of administration or the duration of exposure.

The risk profiling is a methodological approach to systematically integrate all available information on a product’s risks and risk factors. Importantly, the risks to patients, medical personnel or the general public associated with the manufacturing, handling and administration of an ATMP should be evaluated. For CBMPs, for instance, the risk analysis should consider the origin of the cells, the manufacturing process, the cells’ ability to proliferate or trigger an immune response, any non-cellular components as well as the intended therapeutic use. Known risk factors for the class of product could be used for an initial risk assessment; this should be revised and updated as new, product-specific data becomes available throughout the drug’s lifecycle.

Details about the step-wise methodology for risk profiling as well as fictitious examples illustrating the approach are given in the Guideline on risk-based approach for ATMPs (2011). Furthermore, the guidelines outlines how the use of the risk-based approach should be presented in the MAA dossier.

Ultimately, the risk analysis can be used to inform the risk management plan (RMP) which needs to be part of a marketing authorization application (MAA). Further details on the risk analysis of CBMPs are also outlined in the Guideline on Human Cell-based Medicinal Products (2008).

2. Manufacturing (Quality) of ATMPs

a. General aspects

In general, guidelines on the manufacturing or control of biological products either apply directly to ATMPs or can at least offer a good starting point for certain aspects of development of advanced therapy drugs. The scientific guidelines can be found on the EMA website under www.ema.europa.eu > Human regulatory > Scientific guidelines > Biologics.

b. GMP requirements for ATMPs (Annex 2 of GMP guideline)

As mandated in Article 5 of the ATMP Regulation, specific guidelines for Good Manufacturing Practices (GMP) for ATMPs had to be developed. These were included in the EU guidelines for GMP as Annex 2, which applies to biologicals in general (including ATMPs) and came into operation on 31 January 2013 (EU guidelines on GMP, Annex 2 ).

Annex 2 further builds on the notion that biological active substances and medicinal products are to a large extent defined by their manufacturing process which therefore warrants specific regulatory controls. The manufacturing activities that fall within the scope of Annex 2 are illustrated in Table 2.

Certain areas of the manufacturing process of ATMPs, such as the donation, procurement and testing of starting materials for tissue and cell-based products, are covered in other legislations (Directive 2004/23/EC). Similarly, in case where blood and blood components are used as starting materials, Directive 2002/98/EC applies.
Table 2. Illustrative guide to manufacturing activities within the scope of Annex 2. (Source: EU guidelines on GMP, Annex 2).

<table>
<thead>
<tr>
<th>Type and source of material</th>
<th>Example product</th>
<th>Application of this guide to manufacturing steps shown in grey</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Animal or plant sources: non-transgenic</td>
<td>Heparins, insulin, enzymes, proteins, allergen extract, ATMPs, immunosera</td>
<td>Collection of plant, organ, tissue or fluid⁹</td>
</tr>
<tr>
<td>2. Virus or bacteria / fermentation / cell culture</td>
<td>Viral or bacterial vaccines; enzymes, proteins</td>
<td>Establishment &amp; maintenance of MCB¹⁰, WCB, MVS, WVS</td>
</tr>
<tr>
<td>3. Biotechnology - fermentation / cell culture</td>
<td>Recombinant products, MAb, allergens, vaccines</td>
<td>Establishment &amp; maintenance of MCB and WCB, MSL, WSL</td>
</tr>
<tr>
<td>4. Animal sources: transgenic</td>
<td>Recombinant proteins, ATMPs</td>
<td>Master and working transgenic bank</td>
</tr>
<tr>
<td>5. Plant sources: transgenic</td>
<td>Recombinant proteins, vaccines, allergen</td>
<td>Master and working transgenic bank</td>
</tr>
<tr>
<td>6. Human sources</td>
<td>Urine derived enzymes, hormones</td>
<td>Collection of fluid¹²</td>
</tr>
<tr>
<td>7. Human and / or animal sources</td>
<td>Gene therapy: genetically modified cells</td>
<td>Donation, procurement and testing of starting tissue / cells¹⁴</td>
</tr>
<tr>
<td></td>
<td>Somatic cell therapy</td>
<td>Donation, procurement and testing of starting tissue / cells¹⁴</td>
</tr>
<tr>
<td></td>
<td>Tissue engineered products</td>
<td>Donation, procurement and testing of starting tissue / cells¹⁴</td>
</tr>
</tbody>
</table>

⁹ See section B1 for the extent to which GMP principles apply.
¹⁰ See section ‘Seed lot and cell bank system’ for the extent to which GMP applies.
¹¹ HMPC guideline on Good Agricultural and Collection Practice - EMEA/HMPC/246816/2005 may be applied to growing, harvesting and initial processing in open fields.
¹² Principles of GMP apply, see explanatory text in ‘Scope’.
¹³ Where these are viral vectors, the main controls are as for virus manufacture (row 2)
¹⁴ Human tissues and cells must comply with Directive 2004/23/EC and implementing Directives at these stages.
c. Starting and raw materials for ATMPs

Starting materials are defined as “all the materials from which the active substance is manufactured or extracted. For biological medicinal products, starting materials shall mean any substance of biological origin such as micro-organisms, organs and tissues of either plant or animal origin, cells or fluids (including blood or plasma) of human or animal origin, and biotechnological cell constructs (cell substrates, whether they are recombinant or not, including primary cells).” (Annex I, Part I, Module 3, of Directive 2001/83/EC).

For biological medicinal product (including ATMPs) the origin and history of starting materials needs to be described and documented. Since terminal sterilization is generally not feasible, stringent sourcing requirements and acceptance criteria apply for materials derived from humans or animals.

Generally, raw materials are materials used during the production of a medicinal product but which do not form part of the active substance. In the case of cell-based or gene therapy products, often biologically active raw materials such as serum, cytokines, enzymes (e.g. trypsin), antibodies or growth factors have to be employed. It is said that an ATMP is as good as the quality of the starting and raw materials (Salmikangas, 2014); however, these raw materials are often only available at research grade and their quality, safety and consistency is difficult to assess.

Consequently, the acceptability of raw materials in the production of ATMPs often raises questions by both developers and regulators, as they have a critical impact on the ultimate product quality. Recognizing these challenges and the current lack of harmonization, the European Pharmacopoeia (Ph.Eur.) Commission had set up a working party on Raw Materials for the Production of Cellular and Gene-Transfer Products Working Party (RCG WP) to develop appropriate standards. To this end, a stakeholder meeting took place in January 2013, jointly organized by EMA and the European Directorate for the Quality of Medicines and Healthcare (EDQM), to discuss the quality requirements of raw materials for the production of cell-based and gene therapy products (EDQM-EMA Report 2013). Relevant quality attributes of raw material were discussed. The appropriate identification of raw materials, their traceability as well as auditing of raw material providers had been identified as critical aspects for which little guidance exists. The goal of the symposium was to guide the development of harmonized quality requirements for ultimate publication in the Ph.Eur. In October 2014, a new Pharmacopoeia chapter on “Raw materials for the production of cell-based and gene therapy medicinal products” has been released for public consultation (Pharmeuropa 26.4).

A detailed description of all requirements for starting is beyond the scope of this handbook; for further details regarding starting materials of gene therapy products (GTP) or cell-based medicinal products (CBMP) see the Guideline on Human Cell-based Medicinal Products (2008) as well as Annex I, Part I of Directive 2001/83/EC (section Module 3, 3.1 Specific requirements for advanced therapy medicinal products). A useful reference is also the EDQM’s European Guide to the Quality and Safety of Tissues and Cells for Human Application (1st edition) (EDQM 2013). It provides “state-of-the-art information in order to maximise the quality and minimise the risks during donation, procurement, testing, processing, preservation, storage and distribution of tissues and cells”.
d. Donation, procurement and testing

As for any other medicinal product, the quality of ATMPs needs to be insured; as biologicals, this specifically includes the prevention of transmissible/communicable/infectious diseases from cell or tissue donor to recipient. Therefore, a number of specific requirements need to be considered particularly at the start of the manufacturing process of ATMPs. The donation, procurement and testing of human tissues and cells has already been regulated on a EU-wide basis since 2004 (Directive 2004/23/EC), and certain technical requirements have been added later on (Directive 2006/17/EC). The directive is intended to establish EU-wide standards of quality and safety for cell-based medicinal product and a high level of health protection. The principles of this legislation apply to industrially manufactured cell-based ATMPs and are further complemented in the ATMP Regulation (the use of human cells or tissues for research purposes such as in vitro experiments or animal models is not covered by this directive). Of note, also processing, preservation, storage and distribution are regulated elsewhere (Directive 2001/83/EC). Furthermore, Directive 2004/23/EC specifically excludes organs, tissues or cells of animal origin.

The directive mandates that Member States set up systems for the supervision of procurement of human tissues and cells. Establishments involved in the donation or testing of cells or tissues need to be accredited, licensed or authorized, and the respective activities performed by people with appropriate training and experience. Also, a quality management system needs to be in place in accordance with the provisions of Directive 2004/23/EC, and a responsible person needs to be designated. Critically, the directive also specifies the relationship between the tissues establishment and third parties that might be involved in any activity that could influence the quality or safety of the donation. The compliance of these institutions or individuals with the requirements of the directive has to be verified by inspections of the competent authorities.

Tissue establishments shall maintain records of all their activities related and submit annual reports to the competent authorities. Importantly, a system to report, investigate, register and transmit any reports of serious adverse events, which may influence the quality or safety of the donation, needs to be set up.

A basic principle of human cell or tissue donations is that they occur voluntarily, without payment and out of altruistic motives and only once informed consent has been provided by the donors or their relatives. This does not only comply with societal and ethical considerations, but is also thought to increase the safety of the donations. Furthermore, careful donor selection combined with appropriate testing of donations (i.e. cells or tissues) can prevent the transmission of diseases or other unwanted effects.

The data security and anonymity of both donors and recipient need to be ensured, especially with regard to health-related information, testing results or the traceability of their donations.

e. Traceability (requirements acc. to Directive 2004/23/EC)

Importantly, for traceability purposes an identification system for human cells and tissues had to be set up by Member States. A single European coding system has been developed, the so call European Registry for Organs, Tissues and Cells (EUROCET, www.eurocet.org). It includes two official reference compendia – one for tissue establishments (TE) and one for products - in a publicly visible database hosted by the EC. The Single European Code (SEC) is an alphanumeric code that includes information about TE, donation number, product code, divisions and expiry date in a standardized
format. The minimum information to be contained in the European Coding System is specified in Annex II of Directive 2006/86/EC.

<table>
<thead>
<tr>
<th>ISO Country Identifier</th>
<th>TE Code</th>
<th>Unique Donation Number</th>
<th>Coding System Identifier</th>
<th>Product Code</th>
<th>Split Number</th>
<th>Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 characters (alphabetic)</td>
<td>6 characters (alpha/numeric)</td>
<td>13 characters (alpha/numeric)</td>
<td>1 character (alphabetic)</td>
<td>7 characters (alpha/numeric)</td>
<td>3 characters (alpha/numeric)</td>
<td>8 characters (numeric)</td>
</tr>
</tbody>
</table>

Figure 1. Format of the Single European Code

f. Combined ATMPs

As stated previously, the overall responsibility for the scientific assessment of combined ATMPs falls to the CAT. However, in cases where the ATMP contains a medical device as an integral part, it must comply with the essential requirements of medical devices or active implantable medical devices and assessed by a Notified Body, as appropriate (Directive 93/42/EEC and Directive 90/385/EEC, respectively). If the non-cellular structural components are not considered medical device, they still need to be appropriately characterised and evaluated for their suitability for the intended use (Guideline on Human Cell-based Medicinal Products 2008).

g. Quality data for certification (minimum set of data)

For details on the certification procedure for SMEs as well as the minimum quality data required for submission, please see chapter 5. Certification of quality and non-clinical data.

3. Non-clinical development of ATMPs

a. General aspects

Medicinal products under development need to be evaluated in a comprehensive non-clinical pharmacology and toxicology program. These studies in animals and in vitro are aimed at characterizing the drug’s pharmacokinetics and pharmacodynamics behavior as well as to predict its safety profile and response in humans. Extensive guidance exists on the regulatory requirements as well as the scientific principles to be applied during the nonclinical evaluation of medicinal products (www.ema.europa.eu > Human regulatory > Scientific guidelines > Non-clinical).

Given the great variability and unique characteristics of cell-based medicinal products, however, it is acknowledged that conventional non-clinical pharmacology and toxicology studies may not be appropriate for this type of products. Nevertheless, a certain number of non-clinical studies are required in order to demonstrate the product’s proof-of-principle, to characterize its pharmacological and toxicological effects in animals, to support the dosing and treatment duration in humans and to identify potential target organs of toxicity (Guideline on Human Cell-based Medicinal Products 2008).

As with biological medicinal products in general, CBMPs should be tested in relevant animal models; i.e. in animal species where the test material is pharmacologically active (ICH S6 - Preclinical Evaluation of Biotechnology-derived Pharmaceuticals). If appropriate in vivo models are not available,
it might be replaced with appropriate in vitro data. In any case, the chosen development strategy should be adequately justified.

The pharmacological activities of the CBMP in the animal should be demonstrated using markers of biological activity adequate for the intended use of the product (e.g. functional tests for TEP intended for tissue regeneration).

The goal of the non-clinical (pharmacological) testing should be to establish the minimal or optimal effective amount of CBMP needed in order to achieve the desired effect.

b. Non-clinical data for certification (minimum set of data)

For details on the certification procedure for SMEs as well as the minimum non-clinical data required for submission, please see chapter 5. Certification of quality and non-clinical data.

4. Clinical development of ATMPs

a. General considerations

An advanced therapy drug candidate that is being evaluated in clinical trials is defined as an advanced therapy investigational medicinal product (ATIMP). The regulatory framework for the conduct of clinical trials in the EU is the clinical trials guidelines compiled in Volume 10 of the Rules Governing Medicinal Products in the European Union (EudraLex). These guidelines apply to all drugs under investigation; however, certain adaptations are necessary to account for special characteristics of ATIMPs.

- Biodistribution, dose finding
- Route of administration – often surgical procedures that impact on the ATIMPs safety and efficacy
- Study design – double blind trials often not feasible (either no appropriate comparator, or no blinding possible (e.g. surgical procedure))
- Specific endpoints (especially for TEPs – how to measure functional and structural aspects of repaired, regenerated or replaced tissue?)
- Combined ATMPs – functionality of device component to be demonstrated
- Long-term follow-up for safety and efficacy

However, despite all these recognized challenges, a MAA still needs to include convincing safety and efficacy data from prospective clinical trials.

b. GCP requirements for ATMPs (Commission detailed guidelines)

Like any other medicinal product, clinical trials with ATMPs need to adhere to international ethical and quality standards known as Good Clinical Practice (GCP) guidelines. In addition to the Guideline for Good Clinical Practice (E6) of the International Conference on Harmonisation (ICH), GCP principles have been codified in European legislation in the so call “GCP Directive” (Directive 2001/20/EC). These guidance documents set out the standard requirements and procedures for the conduct of clinical trials and ensure that the rights, safety and well-being of trial subjects are protected. Aspects covered include specifications for key documents like the study protocol and the investigator’s brochure (IB), the delineation of sponsor and investigator responsibilities, the need to obtain informed consent from subjects prior to participation in any clinical investigation to the
procedures for obtaining initial authorization from concerned regulatory bodies and ethics committees and how to notify these parties of any changes to the study conduct. All these requirements fully apply to ATMPs.

However, again the special nature of these complex biological drugs makes additional standards/measures necessary to safeguard clinical trial subjects and to ensure the scientific integrity of the trials. The special nature of ATMPs that need to be addressed in clinical trials is reflected in a detailed GCP guideline applicable to clinical studies with advanced therapies. This guideline has been drawn up by the European Commission (EC) in 2009 to capture supplemental GCP principles to be considered for ATMPs (Guidelines on GCP for ATMPs).

In addition to setting quality standards for ATMPs by making reference to the GMP guidelines and Directive 2004/23/EC, the ATMP GCP guideline defines some overarching principles for the clinical development of ATMPs:

- **Traceability** of ATMPs

  Traceability is defined as “the ability to locate and identify each individual unit of tissue/cell during any step from procurement, through processing, testing and storage, to distribution to the recipient or disposal, or vice versa” (…). It also covers the identification of all involved facilities or establishments as well as relevant data on products and materials coming into contact with those tissues/cells during their procurement, processing, testing or storage.

  The traceability mandated for clinical trials falls under the responsibility of the sponsor, the manufacturer and the investigator/institution where the ATIMP is being used and should be described in the study protocol. To ensure full bidirectional traceability (i.e. from source to subject and from subject to source), the system used in the clinical setting explicitly has to be complementary to and compatible with the system in place for the manufacturing of ATMPs (see Section III, 2.e. Traceability (requirements acc. to Directive 2004/23/EC)). Furthermore, the traceability systems should integrate the requirements for drug/IMP accountability.

  - **The chain of custody** of the ATIMP from donation to subject application should have as few links as possible.

  The roles and responsibilities in implementing the traceability system need to be clearly defined and contractually agreed between all parties involved in the handling of the ATIMP – from tissue/blood establishment and procurement organization over manufacturers of the ATIMP, the trial sponsor as well as the investigator/institution. Importantly, the traceability systems need to be maintained even in case of suspension or premature termination of a clinical trial, the discontinuation of the overall development program or in case of transfer of ownership. Should a trial sponsor go bankrupt or cease to exist for other reasons, the traceability records shall be transferred to the national competent authority.

  Importantly, full traceability from donor to recipient needs to be based on an **anonymous coding system** in order to comply with personal data protection requirements (Directive 95/46/EC).

  - **Long-term follow-up** of subjects also beyond the duration of the clinical study

  General reporting requirements for adverse reactions apply to ATMPs; particular emphasis should be placed on training investigators on safety issues of particular concern such as adverse events related to product application (e.g. surgical procedure), cases of infection, hypersensitivity and other unexpected
reactions, adverse reactions related to concomitant medication such as immunosuppression as well as the reactions related to the medical device component of an ATIMP.

Long-term follow-up should be implemented depending on the nature of the ATIMP and in accordance with the guidance on risk assessment and follow-up. The follow-up period should consider the protection of subjects (clinical follow-up) as well as the collection of data (e.g. safety and efficacy follow-up).

In contrast to clinical trials with conventional drugs, all subjects in an ATIMP trial need to receive an **subject alert card** with information about the advanced therapy treatment received.

In addition, the Guidelines on GCP for ATMPs list further responsibilities of investigators and sponsors of ATIMP trials. Furthermore, additional requirements for investigator’s brochure and study protocols for ATIMPs are outlined, as well as essential documents such as traceability records, a tissue/blood establishment file and the follow-up strategy. Further details on the necessary information to be kept in the **traceability records** are listed in the annex of the guideline.

- Tissue establishments may perform processing activities before transferring cell lines to manufacturers.
- For tissues or cells of animal origin sourcing, procurement and testing should be done in accordance with Annex 2 of the GMP guidelines.
- Medical care and medical decisions on behalf of subjects should always be under the responsibility of qualified physicians, even if he is advised by an expert representing the sponsor.

c. Clinical aspects related to TEPs

As a supplement to the *Guideline on Human Cell-based Medicinal Products* (2008) the CAT has also published a reflection paper specifically related to the clinical testing of tissue-engineered products (TEP) and combined TEPs (*Reflection Paper on clinical aspects of TEPs*).

TEPs are intended for the regeneration, repair or replacement of human tissues and many principles of clinical development that apply to traditional medicinal products need to be adjusted to allow for this intended use. For instance, **clinical endpoints** should consider tissue functionality and structural aspects of the regenerated, repaired or replaced tissue. As for any other medicinal products, novel endpoints need to be validated in a prospective study before their use in confirmatory/pivotal trials. Any therapeutic claims need to be based on predefined parameters (including full or partial regeneration, repair or replacement).

According to the reflection paper, pharmacodynamic (PD) addresses the functionality of a TEP, while pharmacokinetic (PK) describes the longevity, biodistribution and degradation of the product and its components.

Further aspects where TEP-specific guidance is given are dose selection, blinding, the choice of comparator as well as the duration of clinical trials. Concomitant treatments or procedures as well as clinical safety considerations are also specified.

Issues related to the development and MAA of **stem cell-based medicinal products** are described in a separate guidance document (*Reflection paper on stem cell-based medicinal products*). Although they share their self-renewal potential, stem cell-based medicinal products is still a rather heterogeneous group of drugs with different levels of scientific knowledge and clinical experience and thus varying
levels of risks associated with their clinical use. The reflection paper addresses quality, non-clinical as well as clinical considerations. It is relevant for all stem cell-based medicinal products, regardless of their level of differentiation.

d. Scientific guidelines (gene therapy; cell & tissue therapies)

A number of scientific guidelines have been issued by the CAT or other EMA bodies that provide guidance of specific aspects of ATMP development. The following is a list of these guidelines available as of [August 2014] on the EMA website under www.ema.europa.eu > Human regulatory > Advanced therapies > Scientific guidelines.

A detailed description of each guideline is beyond the scope of this handbook; however, manufacturers of ATMPs are encouraged to carefully review the available guidance documents and to routinely check the EMA website for new publications or revisions of existing documents.

Table 3. Overview of scientific guidelines for ATMPs.

<table>
<thead>
<tr>
<th>Topic</th>
<th>Reference</th>
<th>Publication date</th>
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<tbody>
<tr>
<td>Gene therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells</td>
<td>Adopted guideline CHMP/GTWP/671639/2008</td>
<td>May 2012</td>
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<tr>
<td>Questions and answers on gene therapy</td>
<td>Adopted guideline CHMP/GTWP/212377/08</td>
<td>Dec 2009</td>
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<tr>
<td>Revision of the note for guidance on the quality, preclinical and clinical aspects of gene transfer medicinal products</td>
<td>Concept paper CHMP/GTWP/234523/09</td>
<td>Release for consultation Dec 2009</td>
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<tr>
<td>ICH Considerations General Principles to Address Virus and Vector Shedding</td>
<td>Concept paper CHMP/ICH/449035/09</td>
<td>July 2009</td>
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<tr>
<td>Quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors</td>
<td>Adopted guideline CHMP/GTWP/587488/07</td>
<td>June 2010</td>
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<tr>
<td>ICH Considerations - Oncolytic Viruses</td>
<td>Adopted guideline CHMP/GTWP/607698/08</td>
<td>Oct 2009</td>
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<tr>
<td>Non-clinical studies required before first clinical use of gene therapy medicinal products</td>
<td>Adopted guideline CHMP/GTWP/587488/07</td>
<td>May 2008</td>
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### Topic

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### Cell therapy and tissue engineering

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<td>Reflection paper on stem cell-based medicinal products</td>
<td>Adopted reflection paper CAT/571134/09</td>
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<td>Adopted guideline CHMP/BWP/271475/06</td>
<td>Dec 2007</td>
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<td>Guideline on xenogeneic cell-based medicinal products</td>
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<td>June 2008</td>
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### e. Clinical trial authorization (CTA)

#### i. General

Prior to starting a clinical trial a sponsor needs to apply for a clinical trial authorization (CTA) with the national competent authority in the Member State(s) in which the study is taking place. The principles for the CTA procedure are aligned across the EU in the so call Clinical Trials Directive (Directive
The legislation for clinical trials has undergone a dramatic change when the **Clinical Trial Regulation** (Regulation (EU) No 536/2014) entered into force which repeals the directive of the same name. Once the regulation applies (no earlier than 28 May 2016) it will further harmonized the requirements for the conduct and authorization of clinical trials across Europe.

A detailed description of the current CTA process is beyond the scope of this handbook; however, the following sections will highlight aspects that are specific to CTAs for ATMPs.

**ii. Specific requirements for ATMPs (e.g. assessment timelines; availability of EMA/CAT certification)**

The Clinical Trial Directive allows for longer assessment periods by regulatory agencies in case of clinical trial applications for ATMPs. The period for the evaluation of the contents of a valid CTA by the competent authority is 90 days for SCT, gene transfer medicinal products as well as genetically modified organisms (GMO). For these products, an additional 90-day extension may be warranted in case a consultation of a group or a committee in accordance with the national regulations of the Member States is considered necessary. For xenogenic cell therapies, no specific limits are stipulated.

The review period for the re-submission of the CTA from the sponsor (addressing any potential agency concerns or recommendations) may be extended from 15 to 30 days in case of ATMPs. A schematic depiction of the CTA process as applicable in Germany is given in Figure 2.

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**Figure 2. Periods and process of clinical trial authorizations – Example Germany** (Source: Paul-Ehrlich-Institute, Germany; www.pei.de)
In accordance with the Guidelines on GCP for ATMPs, the competent authority when reviewing a CTA for an ATIMP trial, will in particular assess the adequateness of the traceability system, the proposed follow-up strategy as well as the end-of-trial definition and risk assessment.

As mentioned, having sought a CAT recommendation on the ATMP classification may facilitate the CTA process on Member State level.

iii. First-in-human trials

For gene therapy medicinal products, a guideline has been issued that outlines the minimal requirements for nonclinical studies to support the first clinical use of GTMPs in human subjects (Guideline on non-clinical studies for gene therapy medicinal products 2008). GTMP-specific aspects regarding the pharmacodynamics “proof of concept” in nonclinical models, biodistribution, establishing the safe starting dose in humans as well as toxicology studies are being addressed. Depending on the proposed clinical use (e.g. paediatric use), integration studies might also be requested. Furthermore, aspects such as target tissue selectivity, immunogenicity/immunotoxicity, reproductive and genotoxicity need to be considered, as well as environmental risk.
Section IV. – Marketing Authorization

As stipulated in the ATMP Regulation, marketing authorization for advanced therapies has to be applied for via the centralized procedure (CP) at the EMA. In general, the standard CP practices and requirements apply and that data as outlined in Annex I of Directive 2001/83/EC needs to be submitted in the marketing authorization application (MAA). However, again a few specific modifications/amendments had to be set down to account for the unique nature of ATMPs. For instance, it is not the Committee for Medicinal Products for Human Use (CHMP), but the Committee for Advanced Therapies (CAT) that is primarily responsible for the scientific evaluation of the application for an ATMP. Furthermore, some specific requirements exist for the summary of product characteristics (SmPC) and a modified assessment timetable applies.

It should be pointed out, however, that obtaining marketing authorization does not guarantee immediate access to the European markets. In most European countries, licensed medicinal products also need to undergo national pricing and reimbursement (P&R) procedures (the so-called “fourth hurdle” to market access). In contrast to the harmonized marketing authorization procedures, pricing and reimbursement systems in the EU are purely national responsibilities and requirements can be vastly different. While a detailed description of P&R systems in EU Member States goes beyond the scope of this handbook, it should be pointed out that the first centrally authorized ATMPs have experienced significant difficulties in obtaining reimbursement agreements in a broad range of countries. Further post-authorization clinical trials are often necessary, not only to fulfil obligations of regulatory approvals (e.g. as part of a conditional marketing authorization), but also to guarantee access to the targeted patients across the EU. Therefore, these efforts need to be considered in the investment needed to develop an ATMP.

1. MAA procedure for ATMPs (incl. assessment timetable)

The details of the MAA evaluation procedure specific to ATMPs, the roles of the various agency stakeholders as well as guidance to the applicant are outlined in a procedural guidance document (Procedural advice on the evaluation of ATMPs 2009).

In summary, the MAA of an ATMP is primarily evaluated by two groups – the CAT Rapporteur’s and the CAT Co-Rapporteur’s assessment teams. Each group includes matter experts for the various disciplines (e.g. quality, safety, efficacy, Pharmacovigilance etc.) as well as a CHMP coordinator. The teams are appointed based on the best available expertise for the ATMP under assessment. The CAT (Co-)Rapporteurs and CHMP coordinators jointly draft the assessment reports (AR) to be circulated to all committee members as well as the applicant.

The CAT is responsible for overall scientific assessment of the application, including the drafting of the milestone ARs (e.g. D120 List of Questions, D180 List of Outstanding Issues); however, critical aspects of the MAA are being discussed at the CHMP, and comments from CHMP as well as other involved working parties are being taken into consideration. The outcome of the CAT’s assessment is a draft opinion on the ATMP’s quality, safety and efficacy, which is forwarded to the CHMP. Based on the CAT opinion, the CHMP adopts a final scientific opinion on the granting, variation, suspension
or revocation of a marketing authorization. This recommendation is then sent to the European Commission (EC) for a decision binding in all Member States. In case the CHMP disagrees with the CAT’s draft opinion, a clarification meeting will be organized by the EMA in order to resolve any divergences prior to the adoption of the final opinion by CHMP.

Importantly, the assessment of an ATMP marketing authorization application is being assessed according to a specific timetable. Adherence to these preset procedural timelines allows for the proper coordination of the multiple stakeholders and their tasks that are required during the MAA assessment. The timetables including the monthly deadlines for submission, start of procedure as well as other milestones of the CP are published on the EMA’s website under www.ema.europa.eu > Human regulatory > Pre-authorisation > Submission dates > Timetables > Timetable: Advanced therapy medicinal products – Full application.

2. Specific dossier requirements for ATMPs

a. SmPC, labeling, package leaflet (specific requirements for ATMPs)

An integral part of a drug’s marketing authorization is the summary of product characteristics (SmPC). From the SmPC, information in lay terms is derived to be included in the package leaflet. Together with the label information (i.e. the text on the immediate container/primary and secondary packaging of the commercial product) the SmPC and PL is appended to the decision of the European Commission (Annex I – III to the Commission Decision). The content and structure of those documents is standardized for all drugs and predefined in Directive 2001/83/EC. However, due to the special nature of ATMPs, specific information requirements are stipulated in the ATMP Regulation (Articles 10–13): Annex II lists the information to be provided in the SmPC of an ATMP; Annex III indicates the information to be provided on immediate and outer packaging, and Annex IV the specific requirements for the package leaflet. Importantly, the unique donation and product codes need to be included on the labeling for traceability purposes.

These specific rules for the labeling of ATMPs aim to combine the patients’ right to know the origin of their tissue- or cell-based therapies, while at the same time respecting the anonymity of the donor.

Of note, annotated templates for the SmPC, labeling and package leaflet are made available by the Quality Review of Documents (QRD) group on the EMA website (www.ema.europa.eu > Human regulatory > Product information > Templates > Centralised procedures).

b. Environmental risk assessment

As for any medicinal product, the MAA for an ATMP needs to include an environmental risk assessment (ERA). General guidance is provided in the Guideline on the ERA of medicinal products for human use (2006). For GTMPs a specific guidance has been issued that outlines the scientific principles and methodology for the ERA (Guideline on ERA for GTMPs).

3. Combined ATMPs and Notified Bodies

As indicated above, in case of combined ATMPs the device component of the medicinal product must also comply with the essential requirements stipulated in Annex I of the Medical Device Directive

During the evaluation of an MAA for a combined ATMP, the CAT may therefore consult the Notified Body (NB) for the assessment of the device part of the advanced therapy, especially when the results of the conformity assessment are not yet included in the MAA dossier. Specific timelines ensure that the conformity assessment of the medical device component is performed in a timely manner and in alignment with the MAA review timetable. The CAT will consider the results of the conformity assessment of the devices part in the overall benefit-risk assessment of the combined ATMP.

For instances, the NB may be consulted in cases where the devices component has a different intended use in the combined ATMP than the use previously assessed by the NB. Also, the combination with the ATMP may alter the original technical, biological or clinical characteristics of the device and therefore necessitate/warrant another assessment of the safety and performance of the device. The details of the interaction between CAT and NB during the assessment of a combined ATMP are outlined in a CAT guidance document (Procedural advice on evaluation of combined ATMPs 2010).

The EMA will select the NB in consultation with the applicant, who will also be included in any interaction between the agency and the NB. A list of NBs including the tasks for which they have been notified is published on EC website under the Nando (New Approach Notified and Designated Organisations) information system (http://ec.europa.eu/enterprise/newapproach/nando/index.cfm). Of note, the applicant of the ATMP marketing authorization application is responsible for paying all applicable fees to the NB for any work performed with regard to the MAA review of the product. With regard to the data requirements for the gene or cell-based component, the data requirements of Directive 2001/83/EC need to be met.

For devices classified as high risk, Part 2 of the former Global Harmonization Task Force (GHTF) guideline (GHTF SG1 N11: 2008 Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) should be followed. In the meantime, the GHTF has been replaced by the International Medical Device Regulators Forum (IMDRF) and the previous GHTF documents have been archived at www.imdrf.org.

If possible, the NB assessment of the device component should use the format and principals of the NBOG (Notified Body Operations Group) guidance on Design – dossier examination and Report Content (http://www.nbog.eu/resources/NBOG_BPG_2009_1.pdf). Information on the device itself as well as the NB assessment, if available, should be included in Module 3, section 3.2.R under “medical device”.

In case the medical device manufacturer is a separate legal entity than the combined ATMP applicant, the latter has to make sure that appropriate agreements are in place that allow the EMA/CAT access to any data on the medical device as deemed necessary for the MAA assessment. Furthermore, the ATMP applicant has to ensure that he will always be informed of any changes of the devices component or any safety issues related to the medical device component.

Especially in cases where the medical device part is not also marketed separately, the burden of having two separate evaluation/assessment procedures for combined ATMPs is considered significant by stakeholders (EC Report COM (2014) 188 final).
Section V. – Post-marketing requirements

1. General post-marketing requirements

As for any medicinal product, MAHs of approved ATMPs need to comply with all post-marketing requirements stipulated in the European legislation. These include a wide variety of obligations that are aimed at ensuring that the marketing authorization dossier for the drug is always up to date and in line with current scientific and technical standards; that data on the safety and effectiveness of the medicinal product – both from post-approval studies as well as from routine use in clinical practice - is continuously collected, evaluated and reported, and ultimately allows for a high-quality benefit-risk management of the medicinal product.

Post-authorization regulatory tools also include the life-cycle management for a drug such as the extension of the approved license for a medicinal product, e.g. by including a new indication or target population. The various regulatory tools are common to medicinal products authorized via the centralized procedure. The requirements are either stipulated by the legislation or derive from product-specific commitments, such as a condition to marketing authorization, an agreed risk management plan (RMP) or paediatric investigational plan (PIP). A detailed description of all post-marketing procedures goes beyond the scope of this handbook; however, the main post-approval activities and obligations can be summarized as follows:

a. Changes to the approved SmPC and/or MAA dossier:
   - Variations and extensions → see 3. Extension of marketing authorization
   - Article 61(3) notifications
   - Urgent safety restrictions
b. Fulfilment of regulatory obligations/conditions/commitments
   - Post-authorization measures (PAM)
   - Renewals
   - Annual re-assessment (of specific obligations - in case of marketing authorization under exceptional circumstances)
   - Annual renewal (in case of conditional marketing authorization)
c. Pharmacovigilance activities
   - ADR reporting
   - Periodic safety update reports (PSUR)
   - Post-authorization safety studies (PASS) / Post-authorization efficacy studies (PAES)
d. Administrative changes and procedures
   - Changing the invented name of a centrally authorized product
   - Transfer of marketing authorizations (MA Transfer) → see 4. Transfer of MA
   - Marketing and cessation notification
   - Sunset clause monitoring
   - Certificates for products

Details of all these procedures and requirements including Question and Answer (Q&A) documents are available on the EMA website under www.ema.europa.eu > Human regulatory > Post-authorisation
2. Post-authorization follow-up of safety and efficacy, and risk management

The marketing authorization of a medicinal product is based on the provision of sufficient data on its quality, safety and efficacy to conclude on a positive benefit-risk balance. However, the need for generating and evaluating long-term safety and efficacy data does not end with the granting of a marketing authorization. The ATMP Regulation emphasizes that the follow-up of efficacy and safety after market entry is a critical aspect for advanced therapies and should account for their complexity and technical specificity. The ATMP manufacturer therefore has to describe in the application for marketing authorization which post-authorization follow-up measures are foreseen. In case of specific risks, an appropriate risk management system needs to be put in place.

In accordance with Article 14(4) of the ATMP Regulation, EMA has issued a detailed guideline on this matter (Guideline on Safety and Efficacy Follow-up - Risk Management of ATMPs 2008). The guideline complements the existing guidance on post-authorization surveillance that applies to medicinal products in general (listed in Appendix I of the guideline) and provides a framework specific to ATMPs. Specific guidelines for GT and CT medicinal products as well as TEPs should be consulted in addition.

The safety and efficacy follow-up systems should be part of the risk management system and captured in the EU risk management plan (RMP). They are defined as “any systematic collection and collation of data that is designed in a way that enables learning about safety and/or efficacy of an ATMP”. They may include passive as well as active surveillance, observational studies, or clinical trials. The guideline also addresses the so-called clinical follow-up, i.e. the follow-up of individual patients that participated in interventional clinical trials with the ATMP.

The guideline extensively describes the scientific rationale why specific rules for the post-authorization surveillance of ATMPs are necessary. It even provides a non-exhaustive list of possible safety and efficacy concerns that should be considered for each individual product. Of note, the safety concerns do not only include risks to patients, but also risks to living donors, close contacts as well as specific parent-child risks.

It is recognized that only limited efficacy data may be available at the time of marketing authorization of an ATMP. Therefore, long-term follow-up is needed to assess the product’s efficacy profile such as its functionality in the recipient/patient, the dynamics or sustainability of effect or the quality of the administration procedure. The guideline also includes a number of points to consider in the design of post-authorization clinical trials or observational studies.

Given the nature of ATMPs, it is expected that a risk management system will be required for marketing authorization. The guideline therefore summarizes the additional requirements for ATMPs and how they should be addressed in the RMP. It should be noted that since the publication of the above mentioned EMA guidance on efficacy and safety follow-up and risk management, a new pharmacovigilance legislation has come into force in the EU. This has also led to changes in the content and structure of the RMP. To account for the special nature and potential risks of ATMP, certain modules of the RMP have been adapted for advanced therapies (e.g. Safety Specifications module VII. Identified and potential risks (ATMP)). Therefore, the EMA guidance for ATMPs should
always be read in conjunction with the general Guideline on good pharmacovigilance practices (GVP), Module V – Risk management systems (Guideline on GVP 2014).

The guideline also specifies the consequences of non-compliance with the agreed RMP. Furthermore, a chapter is dedicated to aspects of personal data protection and how they can be reconciled with the requirements for follow-up and traceability systems in a lawful and fair manner. This necessitates that the data subject has given explicit consent, and that the collected data is adequate, relevant and not excessive in relation to the purpose for which the data is processes.

MAHs of approved ATMPs are encouraged to seek scientific advice from the EMA also regarding the further development and lifecycle strategies for their product. Of note, the fee reductions for implemented under the ATMP Regulation do equally apply to advice on the post-approval activities of advanced therapies (see Section II 3. Incentives of the ATMP Regulation).

3. Extension of marketing authorization

Once a drug has been approved, changes to the terms of the marketing authorization can or should be made. The rules for such changes are stipulated in the so-called Variation Regulation (2008). Depending on the type of proposed changes and the associated risks to public health, variations are classified into Type IA, Type IB or Type II. The latter comprises major changes to the original marketing authorization that “may have a significant impact on the quality, safety or efficacy of a medicinal product”. An example of such a change to be classified as Type II could be the addition of a new indication (including a new target population) to the ATMP’s label. Also the update of the SmPC with new safety information that becomes available after the market introduction of the medicinal product (e.g. new adverse reactions (nature and/or frequency), new warnings and precautions etc.) or the inclusion of results from new clinical trials would be classified as a Type II variation.

The Variation Regulation, however, also clarifies that some proposed changes are considered to fundamentally alter the terms of this authorization” and therefore are not being handled as mere variations. For human medicinal products, this is the case for

- changes to the active substance;
- changes to the strength, pharmaceutical form and route of administration.

These changes are to be submitted as an extension application (sometimes referred to as “line extensions”) which is in essence a new MAA procedure with the same assessment timelines; however, the newly authorized product might still use the same (invented) name as the original MA.

The details of the different variation procedures and extension applications are described on the EMA website under www.ema.europa.eu > Human regulatory > Post-authorisation.

4. Transfer of MA

Following the approval of new drug or ATMP, the marketing authorization can be transferred from the current marketing authorization holder (MAH) (i.e the transferor) to another person or legal entity
Importantly, a simple name or address change of the MAH does not require an MA Transfer if it remains the same legal entity.

The EMA website includes a detailed Q&A section on MA Transfers under [www.ema.europa.eu > Human regulatory > Post-authorisation > Transfer of marketing authorizations](www.ema.europa.eu >). The guidance describes the content to be included in a transfer application and how it will be handled. In essence, it has to be demonstrated/confirmed that the new MAH (the transferee of the MAH) has in its possession the complete and up-to-date dossier for the concerned medicinal product, that it meets all the legal requirements for MAHs in Europe (such as proof of establishment within the EEA, naming a Qualified Person for Pharmacovigilance (QPPV)) and that it is willing to take over all the obligations and responsibilities from the transferor (e.g. all paediatric obligations). An implementation date for the MA transfer has to be given.

Of note, when the MA of a designated orphan medicinal products is being transferred, also the orphan designation needs to be reassigned to the new MAH. However, while both transfers – the MA and the orphan drug designation – should take place at the same time, they are separate processes and will be handled in parallel but by different units within the Agency.

Similarly, a change of the (invented) name of the transferred medicinal product can or has to be requested at the same time as the MA transfer, but in a separate variation procedure that will run in parallel.

For further questions not addressed by the EMA’s post-authorization guidance, applicants can submit their questions to a dedicated email address ([matransferquery@ema.europa.eu](mailto:matransferquery@ema.europa.eu)).
Section VI – Approved ATMPs in the EU – Examples

The following section gives a short summary of the development and approval of the four ATMPs authorized in Europe to date. Further details on these medicinal products can be found in the respective European Public Assessment Reports (EPAR) on the EMA website under www.ema.europa.eu > Find medicine > Human medicines > [product name].

Of note, on 18 December 2014 the CHMP, following the positive assessment of the CAT, recommended the first stem-cell therapy and 5th ATMP for approval in the EU (EMA Press release (19 Dec 2014)). Holoclar contains ex vivo expanded autologous human corneal epithelial cells containing stem cells. The CHMP recommended a conditional marketing authorization for Holoclar for the treatment of moderate to severe limbal stem cell deficiency (LSCD) due to physical or chemical burns in the eye in adults. The final decision will now be taken by the European Commission. The applicant of the Holoclar MAA, Chiesi Farmaceutici S.p.A., had received orphan designation for this condition in 2008.

1. ChondroCelect

ChondroCelect was the first ATMP to receive marketing authorization via the centralized procedure on 5 October 2009. It is a TEP containing “characterized viable autologous cartilage cells expanded ex vivo expressing specific marker proteins” that is indicated for the repair of single symptomatic cartilage defects of the femoral condyle of the knee in adults. The demonstration of efficacy in this indication is based on a randomized controlled trial evaluating the efficacy of ChondroCelect in patients with lesions between 1-5 cm² (ChondroCelect SmPC 2014).

ChondroCelect is a cell-based medicinal product formulated as an implantation suspension of approx. 10,000 cells/μl. The autologous cells are procured arthroscopically from a biopsy of healthy cartilage of the patient, expanded ex vivo and subsequently re-implanted in an open knee surgery. The therapeutic goal of the autologous chondrocyte implantation (ACI) is the repair of cartilage defects through the formation of durable, functional cartilage and a reduced risk of developing knee osteoarthritis.

Non-clinical studies with ChondroCelect included combined PK/PD/toxicology studies in the ectopic mouse (nu/nu) model as well as in orthotopic models in sheep and goats. Conventional pharmacodynamic or dose response studies for ChondroCelect in humans have not been performed. Dose selection was based on data from animal studies conducted by the applicant as well as published literature.

The clinical development of ChondroCelect included a multicenter, randomized controlled Phase 3 trial with a 4-year extension phase (data from the first 2 years have been included in the efficacy evaluation of the MAA). Results from a prospective, long-term follow-up study of patients treated with ChondroCelect was submitted as supportive data (N=20 patients). In addition, safety data was available for 334 patients from a compassionate use program.

The comparator in the pivotal Phase 3 trial was the procedure of microfracture in the repair of symptomatic single cartilage lesions of the femoral condyles of the knee. Overall, 118 patients were
included in this trial – 57 in the ChondroCelect arm (of which 6 patients did not receive study treatment as the chondrocytes failed to expand) and 61 in the microfracture control group. The primary objectives of the study included structural (structural repair (histology)) and clinical endpoints (change from baseline in the Knee injury and Osteoarthritis Outcome Score, KOOS).

GCP inspections identified shortcomings related to the amount of missing data on critical parameters of the pivotal trial (e.g. structural endpoint, ICRS II read out), what were raised as a major concerns. While some issues could be resolved during the procedure, overall the GCP non-compliance could not be post hoc rectified.

The results of the histological analysis of structural repair at 12 months were in favor of ChondroCelect; a statistically significant difference for both qualitative and quantitative analysis was observed. However, the endpoint was not defined a priori but only during the conduct of the ongoing study because the original primary efficacy point was considered invalid due to GCP non-compliance. Furthermore, mean change in overall KOOS from baseline to the average of 12 to 18 months were slightly higher for patients in the ChondroCelect group; the results fulfil the predefined criteria for non-inferiority and changes were considered clinically relevant.

Common side effects of ChondroCelect treatment are arthralgia, cartilage hypertrophy, joint crepitation, joint swelling and joint effusion. The main differences in the safety profile of both treatment groups were related to the open knee surgery. Overall, the safety profile of ChondroCelect was considered acceptable.

The applicant, TiGenix NV, had received CHMP scientific advice on quality, non-clinical and clinical aspects of the dossier.

The assessment of the MAA for ChondroCelect started on 20 June 2007. In agreement with the draft positive opinion adopted by the CAT, the CHMP adopted a positive recommendation for approval on 25 June 2009. As any traditional medicinal product, the MAA of ChondroCelect included a risk management plan (RMP). Specific areas of concern to the CAT were:

- Deficiencies in the conduct of the pre-authorization studies and uncertainties related to the result of the submitted single pivotal trial.
- Unknown long-term durability of the product efficacy.
- Benefit/risk of the product is significantly influenced by the level of compliance with the defined procedures throughout the treatment with ChondroCelect, from the biopsy harvest till the correct physiotherapy.

Specific measures of the agreed RMP include an educational program for healthcare professionals (including training material for surgeons, handling of the biopsy harvest, schedule of follow-up of patients and recommended physiotherapy), a controlled distribution system as well as the conduct of further studies to obtain further safety and efficacy data.

2. Glybera

Glybera (alipogene tiparvovec), an adeno-associated viral vector expressing lipoprotein lipase, was the first gene therapy medicinal product (GCMP) to be approved in accordance with the ATMP Regulation. It received marketing authorization on 25 October 2012 for the treatment of adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions (Glybera SmPC 2014). This is a restriction of the
indication initially applied for and is the outcome of a rather unusual marketing authorization procedure. The licensing of Glybera was in fact preceded by two rounds of negative opinions from the CAT and CHMP.

Glybera for the treatment of lipoprotein was designated as an orphan medicinal product in 2004, a disorder with a calculated prevalence of 0.02 per 10,000 in the EU. At the time of marketing authorization, there is was no other orphan medicinal product authorized for a condition related to the proposed indication.

The assessment of the MAA started in January 2010. In June 2011, based on the overall data submitted, the CAT issued a draft negative opinion that was confirmed by the CHMP. In response the applicant requested a re-examination of the negative opinion. The grounds for re-examination were evaluated by an ad-hoc expert group as well as the CAT, who recommended a marketing authorization under exceptional circumstances, arguing that the potential risks of treatment could be addressed in additional post-marketing studies. CHMP, however, the committee who has the ultimate responsibility in scientific decisions of marketing authorization applications, upheld their initial negative opinion and maintain that the submitted data did not satisfy the criteria for marketing authorization.

The final approval of Glybera followed an unprecedented intervention from the European Commission (EC). For the first time, the EC’s Standing Committee of the European Parliament refused to follow the CHMP’s recommendations and requested the CHMP to re-assess the benefit-risk ratio of Glybera in only a subset of patients, namely those with severe or multiple pancreatitis attacks. A further negative opinion by CHMP in April 2012 was considered void since it was not based on a formally adopted draft opinion from CAT. After two more oral explanations by the applicant at the CAT and CHMP, marketing authorization for Glybera was eventually granted for the subset of LPLD patients with pancreatitis, a major complication of lipoprotein lipase deficiency. MA was granted under exceptional circumstances as the condition is too rare to allow for the provision of a comprehensive data package in terms of clinical experience for a full application.

Glybera is subject to additional monitoring, i.e. its clinical use is being monitored even more intensively than other medicines.

The intended therapeutic effect of Glybera is based on the restoration of the deficient LPL function by transferring copies of the over-functional LPL gene into muscles cells of patients with LPLD. Proof of principle for the treatment of LPLD has been analyzed in two studies using LPL deficient (LPL-/-) mice and cats, respectively. Pharmacology studies indicated that a single administration of Glybera results in long-lasting reduction of triglycerides with expression of the human transgene in animals. With regard to the ATMP’s tumorigenic potential and other risks, CAT and CHMP agreed that overall the data do not substantiate a concern and there were no objections to the approval of Glybera based on review of the non-clinical data.

No conventional PK/PD studies were conducted with Glybera. This was acceptable for a gene-therapy product and the rare orphan condition. The available data on biodistribution / shedding was considered adequate.

Originally applied for indication: “Glybera is indicated for the long term correction of lipoprotein lipase deficiency, to control or abolish symptoms and prevent complications in adult patients clinically diagnosed with lipoprotein lipase deficiency (LPLD)”.
The clinical program consisted of two observational studies and three uncontrolled, open-label interventional studies. In total, 27 patients with LPL deficiency received the study medication and subsequently entered a LPLD patient registry. The efficacy of Glybera was assessed based on the reduction in blood fat levels. The data on LPL activity in human serum was, however, considered inconclusive, CAT and CHMP concluded that the ATMP failed to show a consistent long-lasting, clinically relevant benefit that would outweigh the potential risks of treatment. Glybera was considered reasonably well tolerated in terms of local reactions after multiple intramuscular injections; however, uncertainty exists regarding potential risks such as tissue damage due to inflammatory and degenerative changes in the injected muscles, immunologically relevant risks such as the clinical effects of anti-LPL antibodies. Overall, the safety database in this ultra-rare disease is very limited (N= 27 patients) which makes a conclusion on Glybera’s safety difficult.

The applicant, Amsterdam Molecular Therapeutics (AMT) B.V.\(^5\), had three protocol assistance meetings with CHMP between 2004 and 2009 on the quality, non-clinical and clinical aspects of the dossier.

3. MACI

MACI contains matrix-applied characterized autologous cultured chondrocytes and was the first combined ATMP to receive EU-wide marketing authorization. It was approved in June 2013 for the repair of symptomatic, full-thickness cartilage defects of the knee (3-20 cm\(^2\)) in skeletally adult patients (MACI SmPC 2014). As Glybera, MACI is subject to additional monitoring.

MACI is a third generation autologous chondrocyte implantation (ACI) product where autologous chondrocytes are seeded onto a collagen membrane of porcine origin, which is secured into the lesion with fibrin glue.

The main clinical trial supporting the MA of MACI was a prospective, randomized, open-label parallel-group study (“Superiority of MACI Versus Microfracture Treatment”, SUMMIT). The aim of this trial was to demonstrate the superiority of MACI implant versus arthroscopic microfracture for the treatment of symptomatic articular cartilage defects of the femoral condyle, including the trochlea. It included 144 patients – 72 of which were treated with MACI and 72 received microfracture treatment as a control. In the co-primary endpoint KOOS (knee injury and osteoarthritis outcome score) for Pain and Function, a clinically and statistically significant difference was seen at week 104 in favor of MACI. No statistically significant difference was seen between both treatment groups regarding structural endpoints; however, CHMP confirmed that improvements in the clinical outcomes of pain and function remain the most clinically valid endpoints in cartilage repair studies. The results of the primary endpoint were corroborated by several other PRO measures and a responder analysis of the primary efficacy measures.

The application dossier also included published literature of MACI, which has been available in some European countries since 1998.

The known safety profile for MACI, based on the exposure of more than 6,000 patients, includes two main risks: symptomatic graft hypertrophy and graft delamination. Generally, these adverse reactions of interest have not frequently been reported in the studies but the incidence of graft hypertrophy appeared to increase over time. Overall, the safety profile was considered acceptable and manageable.

\(^5\) In July 2012, the applicant for the Glybera MAA was changed to uniQure biopharma B.V.
Educational material for HCP involved in the surgical treatment or follow-up of patients will detail how to recognize the signs and symptoms of important known and potential risks of the product.

The MAH was requested to provide the 5-year follow-up data from the main clinical study (SUMMIT) to provide data on the sustainability of the cartilage repair and maintenance of effect of MACI over time, as well as the long-term safety of the medicine.

The MAA assessment procedure started in September 2011. In April 2013, the CAT issued a positive draft opinion recommending the marketing authorization of MACI. This recommendation was confirmed by CHMP in the same month.

The initial applicant of this MAA, Genzyme Europe B.V., received scientific advice from CAT/CHMP in 2007 and 2010 on the quality, non-clinical and clinical aspects of the dossier.

In August 2014, the marketing authorization of MACI was transferred from Genzyme Europe B.V. to Aastrom Biosciences DK ApS. In September 2014, the MAH of MACI closed the manufacturing site of the medicinal product in Denmark. Therefore, MACI was put on the drug shortages catalogue and is now unavailable for patients in the EU. The site closure was due to commercial reasons, the safety and efficacy of the ATMP has not changed.

As a consequence of this site closure and as part of a so-called Article 20 procedure, the CHMP has been working with the MAH to put arrangements in place that allow existing patients to complete their treatment. The MAH has been requested to store any remaining biopsies to allow for potential future treatment of existing patients. Healthcare professionals were asked not to start new patients on MACI.

4. Provenge

Provenge consists of autologous peripheral-blood mononuclear cells [including a minimum of 50 million autologous CD54+ cells] activated with prostatic acid phosphatase granulocyte-macrophage colony-stimulating factor (PAP-GM-CSF) (sipuleucel-T) (Provenge SmPC 2013). Provenge, which differs from classical dendritic cell (DC) products by short time culture of whole peripheral blood mononuclear cells (PBMC), is designed to break immunological tolerance and stimulate an immune response to the target antigen prostatic acid phosphatase (PAP).

Provenge has been licensed in September 2013 for the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.

The clinical development program of Provenge consisted of 14 clinical trials conducted in the United States and Canada and one Phase 2 study (Study D9906) conducted in Japan.

The pivotal Phase 3 IMPACT trial (D9902B) was one of 3 randomized, double-blind, “placebo-leukapheresis” controlled studies that were part of the application. The study included 512 randomized patients and evaluated overall survival as the primary endpoint. While there was dissociation between the primary and secondary endpoints, the CAT considered the observed effect on overall survival (median survival was 4.1 months longer than in the placebo group) sufficiently convincing, especially since the effect was observed across different trials. Nevertheless, there was concern whether the observed difference in overall survival between both arms was a true treatment effect or rather might have been compounded by subsequent non-study cancer therapies and other biases.
The MAA assessment procedure started in January 2012. In June 2013, the CAT issued a positive draft opinion; this was confirmed by the CHMP that recommended the marketing authorization of Provenge. Of note, Provenge has already been licensed in the US since 2010 for the same indication. While the manufacturer had submitted a biologics license application already in 2006, the BLA was only granted once the results of the Phase 3 study (D9902B) had become available and questions regarding the manufacturing and control of the product had been resolved (FDA, Provenge BLA 2010).

As Glybera and MACI, Provenge is subject to additional monitoring. The applicant, Dendreon UK Ltd, received scientific advice from CHMP in 2008 on the quality and clinical aspects of the dossier.
Section VII. – ATMP regulation outside the EU

1. USA

   a. Legal framework & regulatory procedures at CBER

   The US Food and Drug Administration (FDA) refers to the class of cell- and tissue-based therapeutics as HCT/Ps (human cells, tissues and cellular & tissue-based products). Within the Center for Biologics Evaluation and Research (CBER) the responsibility for these products falls to the Office of Cellular, Tissue and Gene Therapies (OCTGT).

   HCT/Ps are defined as follows (21 CFR 1271.3):

   \[
   \text{HCT/Ps means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue.}
   \]

   The section goes on to list a number of products that explicitly fall not under the definition of HCT/Ps such as vascularized human organs for transplantation, whole blood or blood components, secreted or extracted human products (e.g. milk, collagen), minimally manipulated bone marrow for homologous use or cells, tissues and organs derived from animals other than humans.

   Legislation

   When cellular and tissue-based innovative therapeutics emerged, the key concern was the transmission of communicable diseases. To address these concerns, the FDA adopted a set of rules which are codified in Title 21 of the Code of Federal Regulations Part 1271 (21 CFR 1271). It is based on Section 361 of the Public Health and Service Act (PHS Act) which grants FDA the authority to prevent the spread of transmissible diseases.

   The legislation foresees a tiered and risked-based approach and products are divided into lower risk products (so-called “361 HCT/Ps” – see below) and higher risk HCT/Ps (therapeutic “351 HCT/Ps”) – with the numbers referring to the applicable sections in the PHS Act. At the same time, it was intended to ensure that like products are treated alike and to still allow for innovation.

   After a step-wise introduction, 21 CFR 1271 became fully effective on 25 May 2005. It is structured in subparts A to F:

   \begin{itemize}
   \item **Subpart A:** General Provisions (e.g. scope and purpose of 21 CFR Part 1271, definitions).
   \item **Subpart B:** Procedures for Registration and Listing.
   \item **Subpart C:** Donor eligibility (i.e. provisions for the screening and testing of donors to determine their eligibility).
   \end{itemize}
Subpart D: Current Good Tissue Practice.

Subpart E: Additional Requirements for Establishments Described in 1271.10.

Subpart F: Inspection and Enforcement of Establishments Described in 1271.10.

These sets of rules are intended to prevent the transmission and spread of communicable disease, thus increasing the safety of HCT/Ps and protecting public health while minimizing regulatory burden and encouraging therapeutic innovation.

“361 HCT/Ps” versus “351 HCT/Ps” (drugs, biologics or devices)

21 CFR 1271 established a tiered, risk-based approach to the regulation of HCT/Ps. This means that some low risk HCT/Ps are regulated solely under the provisions of the 21 CFR 1271 rules (as well as section 361 of PHS Act). An establishment registration and product listing is needed; however, no pre-market approval is necessary. In order to be classified as “361 HCT/P” all criteria in 21 CFR 1271.10(a) have to be met:

- HCT/P is minimally manipulated;
- Intended for homologous use as determined by labeling and advertising;
- Its manufacture does not involve combination with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent (not raising new clinical safety concerns for HCT/P);
- It does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function, or if it has such an effect, it is intended for autologous use or allogeneic use in close relatives or for reproductive use.

Examples for “361 HCT/Ps” include bone, cartilage, ligament, cornea, vascular grafts, heart valves, dura mater, as well as reproductive cells and tissues (e.g. semen, oocytes, embryos) - if minimally manipulated, intended for homologous use only, and not combined with another article.

If not all of the 10(a) criteria are met and none of the exemptions for establishments apply (21 CFR 1271.15), the HCT/P is being regulated as a drug, device and/or biologic (“351 HCT/Ps”) under section 351 of the PHS Act (biologics) and/or the Food, Drug and Cosmetics Act (drugs, devices) in addition to the requirements set out by 21 CFR 1271. This means the requirements of the tissue regulations as well as premarket review apply to these higher risk HCT/Ps.

Manufacturers of HCT/Ps may self-determine whether their product fulfills the requirements of a “361 HCT/P” and can be marketed without approval or clearance. However, if in doubt (e.g. whether the “minimal manipulation” or “homologous use” criteria are really met) or to avoid enforcement actions/sanctions, the manufacturer may consult with FDA prior to marketing their HCT/P. Clarification of the jurisdictional determination for a product can be requested from the interdisciplinary Tissues Reference Group (TRG); furthermore, a request for designation (RFD) can be addressed to the Office of Combination Products (OCP).

b. FDA guidance

The principles of 21 CFR 1271 have been implemented in the following rules:
Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing (66 FR 5447, January 19, 2001) (Registration Final Rule 2001)


In addition to the tissue rules, the FDA has issued numerous scientific guidelines for the development of HCT/Ps. They can be found on the FDA website under www.fda.gov > Vaccines, Blood & Biologics > Guidance, Compliance & Regulatory Information (Biologics) > Biologics Guidances > Cellular & Gene Therapy Guidances and > Tissue Guidances.

As outlined above, for HCT/Ps that are classified as biologics, drugs or devices, the regulatory requirements for the manufacture, preclinical and clinical development for the respective class have to be met in addition to the rules in 21 CFR 1271. A detailed review of all these requirements goes beyond the scope of this handbook; however, the FDA’s website provides detailed guidance (www.fda.gov).

c. Parallel scientific advice with EMA

In 2003, EMA and FDA have initiated a formal collaboration under a confidentiality agreement. An ATMP cluster has been initiated in 2008 that meets bi-monthly to exchange views and discuss both general and specific topics. Furthermore, the manufacturer of an advanced therapy (ATMP or HCT/P) can also benefit from a parallel scientific advice with EMA and FDA. This procedure, which has been initiated in 2009 and usually occurs via phone or video conference, is limited to certain types of products of specific interest, and explicitly includes advanced therapies.

The intention of these parallel procedures is to increase the dialogue between the agencies and the applicant and provide a mechanism for exchanging views on scientific issues during the drug’s development. Both agencies have agreed to a set of general principles related to the parallel scientific advice procedure. Notably, the goal of the procedure should be on “sharing information and perspectives, rather than specific harmonization of study or regulatory requirements”. This means that while a common, harmonized opinion might be the outcome of the parallel consultation, it is not a stated goal of the procedure. However, it should in any case clarify to the sponsor the divergent views or opinion where they exist.

The applicable fees are the same as for a standard scientific advice with EMA; interactions with FDA during the development phase of a medicinal product are free of charge.
References

1. Regulations, Directives & Guidelines


ChondroCelect SmPC. Summary of Product Characteristics ChondroCelect. 2014.


German Drug Law. "Arzneimittelgesetz (AMG) (German Drug Law)." n.d.


MACI SmPC. "Summary of Product Characteristics MACI." 2014.


Procedural advice on evaluation of combined ATMPs. Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007. 2010.

Procedural advice on the evaluation of ATMPs. PROCEDURAL ADVICE ON THE EVALUATION OF ADVANCED THERAPY MEDICINAL PRODUCT IN ACCORDANCE WITH ARTICLE 8 OF REGULATION (EC) NO 1394/2007. 2009.


2. **Important websites**

- European Medicines Agency (EMA) www.ema.europa.eu → Human regulatory → Advanced-therapy Medicinal Products
  → Volume 1 – EU pharmaceutical legislation for medicinal products for human use
  → Volume 2 – Notice to applicants and regulatory guidelines for medicinal products for human use
  → Volume 3 – Scientific guidelines for medicinal products for human use
  → Volume 4 – Guidelines for good manufacturing practices for medicinal products for human and veterinary use
  → Volume 9 – Guidelines for Pharmacovigilance for medicinal products for human and veterinary use
  → Volume 10 – Guidelines for clinical trials
- US Food and Drug Administration (FDA) [www.fda.gov](http://www.fda.gov)
  **Tissue and Tissue Products** - [http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm](http://www.fda.gov/BiologicsBloodVaccines/TissueTissueProducts/default.htm)
Appendices

The following sections briefly summarize some key regulatory topics in Europe. The descriptions are not meant to be exhaustive; further details can be found under the references provided.

Appendix 1. Regulatory framework & regulatory bodies in Europe

1. Regulatory bodies

a. European Commission

On a pan-European level, the European Commission (EC) is the legislative and decision-making body (www.ec.europa.eu). It is composed of representatives of all EU Member States and structured in several departments (Directorates-General, DG) responsible for special policy areas. Each DG is headed by a Commissioner. Following the general election in May 2014 and the subsequent restructuring, the responsibility for medicinal products still lies with the directorate for Health and Consumers (previously Health and Safety), DG SANCO, while medical devices fall now into the scope of DG GROWTH (Internal Market, Industry, Entrepreneurship and SMEs; formerly DG Enterprise and Industry, ENTR).

It is the EC who ultimately decides on the granting, suspension or withdrawal of a marketing authorization for medicinal products evaluated through the centralized procedures (see Decision making procedure). However, the scientific review and assessment is delegated to a specialized European agency, the European Medicines Agency (EMA) located in London (see 1.b. European Medicines Agency (EMA)).

b. European Medicines Agency (EMA)

The European Medicines Agency (EMA) is an agency of the European Union responsible for the evaluation and supervision of medicines for human and veterinary use (www.ema.europa.eu). Specifically, this includes the scientific assessment of marketing authorization applications (MAA) for products licensed through the centralized procedure, safety monitoring of marketed drugs, evaluation of referrals as well as the coordination of inspections. Furthermore, the EMA also has a central function in the EU telematics program, i.e. the central pan-European systems and databases for medicines.

The scientific work at the EMA is handled by seven scientific committees:

- Committee for Medicinal Products for Human Use (CHMP)
- Pharmacovigilance Risk Assessment Committee (PRAC)
- Committee for Medicinal Products for Veterinary Use (CVMP)
- Committee for Orphan Medicinal Products (COMP)
- Committee on Herbal Medicinal Products (HMPC)
- Committee for Advanced Therapies (CAT)
- Paediatric Committee (PDCO)
The committees, which are made up of representatives of all EU Member States, are supported by the staff of the EMA secretariat. In addition, each committee can draw expertise from a large number of working parties that are composed of matter experts from across the EU.

The EMA was established in 1995 and is situated in Canary Wharf in the East of London.

c. National competent authorities

In addition to the EMA, each Member State of the EU has its own national competent authority (NCA) responsible for regulating medicinal products for human and veterinary use. These agencies are responsible for granting MAs for medicinal products that are not assessed via the centralised procedure. However, also national MAA procedures are being coordinated across EU countries, either through the so called mutual recognition procedure (MRP) or decentralised procedure (DCP). Those decentralized procedures are supported by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and the Coordination Group for Mutual Recognition and Decentralised Procedures - Veterinary (CMDv).

d. Notified bodies

In contrast to medicinal products, which are evaluated and supervised by NCAs, the conformity assessments of medical devices are overseen by so called notified bodies (NB). Notified bodies are certification organizations which are designated by a Member State to carry out conformity assessment according to the Medical Device Directive. Amongst other tasks, NBs carry out assessment of the manufacturer's quality system, its design dossier and full technical information of a product as well as perform the appropriate testing of a representative sample to ensure that it meets the requirements.

The notification of NBs to the Commission and other Member States as well as their withdrawal is the responsibility of the notifying country.

2. EU Regulations & Directives

a. European and national legislations

Generally, legislation in the EU is based on the principle of subsidiarity; that means, matters are only covered on an EU-level if it considered more efficient than decisions taken on a national or regional level (Article 5 of the Treaty on the European Union). This is the case in many aspects concerning medicinal products; therefore, a wide range of EU legislation related to pharmaceuticals exists, which is compiled in Volume 1 and Volume 5 of the so called Rules governing medicinal products in the European Union (www.ec.europa.eu > DG Health & Consumers > Public health > News and updates on pharmaceuticals > Eudralex). The overarching goals of the EU legislation are the protection of public health and the free movement of medicinal products across the Union’s single market.

Different types of legal acts exist on an EU level. Regulations are binding legislative act that must be applied in its entirety across the EU (such as the ATMP Regulation, for example). Directives, on the other hand, only set out a goal that all EU countries must achieve; however, the actual implementation of the Directive into national law is the responsibility of the individual countries. Therefore, the detailed requirements of the resulting national legislations may vary across different Member States (like in the case of the clinical Trials Directive (Directive 2001/20/EC 2001)).
b. Scientific and procedural guidelines

The EMA’s committees prepare scientific and procedural guidelines on all kinds of topics related to the development, authorization and life-cycle management of a medicinal product. The scientific guidelines are intended to support the manufacturers in meeting the requirements for the demonstration of quality, safety and efficacy of their product. Detailed procedural guidance and practical Question-and-Answer documents assist applicants and MAHs to prepare for and manage all types of submissions and obligations.

The guidelines are developed in consultation with regulatory authorities in the Member States and published on the EMA website (www.ema.europa.eu > Human regulatory > Scientific guidelines). Of note, this website now replaces the former Volume 3 of the rules governing medicinal products in the European Union (EudraLex), published by the European Commission.

Appendix 2. Regulatory procedures in Europe

1. Marketing authorization procedures

a. Centralized procedure (mandatory and optional scope)

Medicinal products must only be placed on the market in the EEA if they have been granted a marketing authorization (MA) either by a Member State by their own territory (national MA) or a Union authorization valid across the entire EU (Union MA) (Article 6(1) of Directive 2001/83/EC). The procedure for granting a Union MA is called the centralized procedure.

Under the centralized procedure, pharmaceutical companies submit a single MAA for scientific evaluation to the EMA. The scientific assessment by the CHMP (in consultation with other relevant committees) evaluates whether the quality, safety and efficacy of the medicinal product has been demonstrated by the applicant. By law, the assessment procedure has to be completed within a maximum of 210 days; it ends with the adoption of a scientific opinion on whether the medicine should be marketed or not. This opinion is then transmitted to the EC who has the authority of granting the official marketing authorization valid across the EU as well as in the countries of the European Economic Area (EEA), Iceland, Norway and Liechtenstein.

As defined in the Annex of Regulation (EC) No 726/2004, the centralized procedure is mandatory for the following products:

- Human medicines for the treatment of human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases;
- Veterinary medicines for use as growth or yield enhancers;
- Medicines derived from biotechnology processes, such as genetic engineering;
- Advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines;
- Designated ‘orphan medicines’ (medicines used for rare human diseases).

An MAA via the centralized procedure is optional for medicinal products that contain a new active substance or that are a significant therapeutic, scientific or technical innovation, or when the
centralized MA would be in the interest of public or animal health. In these cases the applicant may request a MA via the centralized procedure.

The details of the centralized procedure are described in Volume 2A, Chapter 4 of the Notice to Applicants.

b. National MA procedure, MRP, DCP

Products that do not fall within the mandatory scope of the centralized procedure can obtain a national marketing authorization from the concerned Member State. In individual EU Member States the marketing authorization procedure has to be in accordance with national requirements which are based on the EU legal principles. When MA is sought in two or more Member States, the assessment procedures are coordinated via the decentralized or mutual recognition procedures.

- Decentralised procedure

Companies can apply for the simultaneous authorization of a medicinal product in more than one EU country if it has not been previously authorized in any EU country and it does not fall within the mandatory scope of the centralized procedure.

- Mutual-recognition procedure

Companies that already hold a marketing authorization for a medicinal product in one EU Member State (the so-called reference Member State) can ask additional Member States to recognize this MA in order to obtain national authorizations in these concerned Member States.

The details of these decentralized procedures are described in Volume 2A, Chapter 2 of the Notice to Applicants.

2. Special regulatory procedures

a. EMA Unique product identifier (UPI)

In 2014, the EMA introduced the unique product identifier (UPI). It is an individual reference number for a medicinal product that helps to track a pharmaceutical throughout the various pre-authorization procedures. The number will be assigned automatically to all products reaching the Agency for the first time (e.g. in an application for scientific advice or orphan drug designation). The UPI should be included in any correspondence with the EMA on any matter related to this specific medicinal product.

b. Orphan drug designation

Specialized EU legislation has been introduced in 2000 with the goal to incentivize the development of medicinal products for the diagnosis, prevention or treatment of rare diseases, the so-called orphan drugs (Regulation (EC) No 141/2000). The legislation applies to medicinal products which are intended to diagnose, prevent or treat life-threatening or very serious conditions that affect not more than 5 in 10,000 persons in the EU. To be eligible for the incentives of the orphan regulation, medicinal products need to be designated through a Community procedure which may be obtained at any stage of product development prior to its marketing authorization. The EMA, through its Committee for Orphan Medicinal Products (COMP) is responsible for reviewing designation
applications and issuing an opinion, which is transformed into a decision by the European Commission.

Once a designated orphan medicinal product is granted a MA, it is protected by a ten year period of market exclusivity for its ‘orphan indication’, i.e. ‘similar’ medicinal products will not receive a MA for the same therapeutic indication unless the originator gives consent, is unable to supply sufficient quantities of the medicinal product, or the second applicant demonstrates that although similar, the medicinal product is clinically superior to the originator.

Other orphan incentives include assistance with the development of the orphan medicinal product (e.g. total or partial fee reduction for protocol assistance), reduced fees for MAAs and protection from market competition once the drug has been authorized (so-called orphan exclusivity).

Details about the orphan drug designation procedure and the incentives foreseen by the Orphan Regulation can be found on the EMA website under www.ema.europa.eu > Human regulatory > Orphan designation.

c. Accelerated assessment

Manufacturers of medicinal products that are considered of major interest for public health and in particular from the view point of therapeutic innovation may request an accelerated assessment procedure for the product’s MA (Article 14(9) of Regulation (EC) No 726/2004). Upon request from the applicant including justifications that all necessary criteria are met and the Rapporteurs’ recommendations the CHMP will formulate a decision. If the request is accepted, the standard evaluation time for the MAA of 210 days will be reduced to 150 days.

The details of the accelerated assessment as well as a template for requesting an accelerated assessment can be found under www.ema.europa.eu > Human regulatory > Pre-authorisation > Q&A: Presubmission guidance.

d. Conditionals approval, approval under exceptional circumstances

Conditional Approval

For certain categories of medicinal products, in order to meet unmet medical needs of patients and in the interest of public health, it may be necessary to grant marketing authorizations on the basis of less complete clinical data on the safety and efficacy of the medicinal product than is normally required.

In certain cases such as medicinal products used in seriously debilitating or life-threatening diseases, emergency situations in response to public health threats, or products designated as orphan medicinal products, a marketing authorization may be granted on the basis of less complete data than is normally required. If these products meet an unmet medical need and are in the interest of public health a conditional marketing authorization may be granted provided that the following criteria are met:

- The risk-benefit balance of the product is positive;
- It is likely that the applicant will be able to provide comprehensive data;
- Fulfilment of unmet medical need;
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

Conditional marketing authorizations are initially valid for one year and have to be renewed on an annual basis. As a condition of the MA, the MAH will be required to complete ongoing studies or to
conduct new studies to confirm the safety and efficacy of the medicinal product and a positive risk-benefit balance.

For further details on the conditional MA see www.ema.europa.eu > Human regulatory > Pre-authorisation > Q&A: Presubmission guidance.

Approval under exceptional circumstances

In contrast to the conditional MA, where comprehensive clinical safety and efficacy data is expected to be provided post-approval, there may be instances where the manufacturer is unable to provide such comprehensive data under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence, or
- in the present state of scientific knowledge, comprehensive information cannot be provided, or
- it would be contrary to generally accepted principles of medical ethics to collect such information.

In these instances, a marketing authorization may be granted under exceptional circumstances. This includes that the MAH is required to introduce specific procedures, in particular concerning the safety of the product. Continuous validity of the MA will be linked to the annual reassessment of these procedures.

For further guidance on the conditions and procedures for the granting of a marketing authorization under exceptional circumstances, refer to the EMA guidance under www.ema.europa.eu > Human regulatory > Pre-authorisation > Q&A: Presubmission guidance.

e. Adaptive pathways

In order to improve the access of innovative new therapies for patients, the EMA together with collaboration partners and stakeholders has been developing new approaches for drug approval called ‘adaptive pathways’ (also referred to as ‘staggered approval’ or ‘adaptive licensing’). A pilot project has been initiated in March 2014 with interested companies. Step I of this project is expected to finish in February 2015.

For further details see on the new adaptive pathway approaches see www.ema.europa.eu > Human regulatory > Adaptive pathways.

3. Scientific advice procedures

a. Central advice (EMA)

i. Scientific advice / Protocol assistance / Parallel SA with FDA

Manufacturers of pharmaceuticals can seek scientific advice or protocol assistance (for designated orphan drugs) from the EMA on questions relating to the manufacturing, non-clinical or clinical development of the drug. For human medicines, the advice is given by CHMP based on the recommendations of the Scientific Advice Working Party (SAWP). Scientific advice can be requested
at any stage of development of a medicine, regardless of whether the medicine is eligible for the centralized authorization procedure or not. Advice is given on specific questions posed by the company. The advice given is not legally binding.

The standard scientific advice procedure at the EMA is subject to fees which vary depending on the exact scope of the advice being sought. Certain fee reductions apply, e.g. for orphan medicinal products, SMEs or for medicinal products for paediatric use. Furthermore, manufacturers of ATMPs are eligible for a fee reduction when seeking scientific advice from the EMA. At the time of writing, the reduction was 65% of the applicable administrative fees.

Details about the how to request scientific advice at the EMA can be found under [www.ema.europa.eu](http://www.ema.europa.eu) > Human regulatory > Scientific advice and protocol assistance.

**ii. ITF meetings**

The Innovation Task Force (ITF) is a multidisciplinary group of experts that includes scientific, regulatory and legal competences. Similar to the ATMP classification (Section 4.), briefing meetings with ITF offer developers of new drugs or technologies the opportunity for a dialogue with regulators at an early stage of the development.


**iii. SME office**

In accordance with EU legislation, the EMA is providing incentives for micro-, small- and medium-sized enterprises (SMEs) that are developing medicines for human or veterinary use. The goal is to promote innovation and the development of new medicines by SMEs. In this context, the EMA has set up a dedicated SME office that is tasked with offering assistance to SMEs with practical or procedural enquiries, workshops and training sessions for SMEs.

Details on how to apply for SME status as well as the support and guidance provided by the SME office can be found under [www.ema.europa.eu](http://www.ema.europa.eu) > Human regulatory > SME office.

**b. National scientific advice**

In addition to scientific advice sought from the EMA, manufacturers of medicinal products may also engage in a scientific dialogue with any national competent authority. The details of the procedures, timelines and fees vary across Member States and should be clarified on a case-by-case basis. Further information is usually available on the websites of the national regulatory agencies.

**Appendix 3. Marketing authorization procedure**

**1. MAA dossier**

The MA application dossier must be presented in accordance with the internationally agreed common technical document (CTD) format (see Volume 2B of the Notice to Applicants). The EU CTD is organized in five modules: Module 1 contains the specific EU administrative and prescribing information. The structure of Modules 2, 3, 4, and 5 is common for all ICH regions and will contain the high level summaries and quality, non-clinical and clinical documentation respectively.
All MAAs must be submitted in English language. Detailed information on the submission requirements for the EMA, (co-)rapporteur, and CHMP members are given in www.ema.europa.eu > Human regulatory > Pre-authorisation > Q&A: Presubmission guidance;

Of note, since 2010 all electronic MAA submissions to the EMA must comply with the electronic CTD (eCTD) specifications. Furthermore, since March 2014 the use of the dedicated submission channels — either the eSubmission Gateway or the Submission Web Client — has become mandatory for all eCTD submissions through the centralized procedure; submissions on CD or DVD will no longer be accepted. The web-based client is a free tool particularly suitable for SMEs with low transmission volumes.

Further details on eSubmissions to the EMA can be found under http://esubmission.ema.europa.eu.

2. Pre-submission meeting (EMA, Rapporteurs)

Prior to submitting an MAA, applicants can request pre-submission meeting with the EMA secretariat as well as their assigned rapporteurs in order to seek assistance in the finalization of their upcoming filing. The clarification of product-specific legal, regulatory and scientific issues is intended to facilitate the validation and assessment of the MAA; furthermore, it provides an opportunity to establish contacts with the EMA staff that will be involved with the application. Pre-submission meetings for MAAs usually take place 6-7 months prior to the planned submission of an application.

For details about how and when to request a pre-submission meeting including the request form see www.ema.europa.eu > Human regulatory > Pre-authorisation > Q&A: Presubmission guidance.

3. CHMP opinion and Commission decision

Following the scientific assessment of an MAA by the CHMP, the committee’s opinion is being forwarded to the European Commission (EC). In the case of a favorable opinion, the EC will issue a marketing authorization valid throughout the Community. For medicinal products for human use, the Commission is assisted by the Standing Committee on Medicinal Products for Human Use (the “Standing Committee”) in which all EU Member States are represented.

For further details see Chapter 6 Decision Making Procedure for the Adoption of Commission Decisions (Notice to Applicants, Volume 2A, Chapter 6 2005).

4. Data exclusivity; market exclusivity

The period of data exclusivity has been harmonized across Member States in 2005. Since then, innovative medicinal products, once authorized, are protected by the so-called data exclusivity. This means that for a period of 8 years a generic medicinal product may not rely in their abridged MAA on the non-clinical and clinical data of the reference medicinal product (Article 10 of Directive 2011/83/EC). Once the period of data exclusivity has expired, the originator is protected for another 2 years by the market exclusivity, i.e. generic products that have been authorized in accordance with
Article 10 may not be placed on the market until the 10 year protection period is over. This ten-year period can only be prolonged in the case of certain new indications.

For calculating periods of protection the notion of the global marketing authorization applies. This means that the protection periods start with the initial authorization of the medicinal product in the EU and includes all variations and extensions thereof, as well as any additional strengths, pharmaceutical form, administration routes or presentations authorized through separate procedures and under a different name, if granted to the MAH of the initial authorization.

Details about data exclusivity and market protection for pharmaceuticals are described in Chapter 1 Marketing Authorization (Notice to Applicants, Volume 2A, Chapter 1 2013).

Of note, in case where the reference medicinal product is a biologic (or ATMP), the general criteria for generic MAAs do not apply; rather, follow-on biologicals that are similar to the reference product must still provide a certain amount of preclinical and clinical data in support of its MAA. For further details on biosimilars see www.ema.europa.eu > Human regulatory > Scientific guidelines > Multidisciplinary > Biosimilar.