Development of Tissue Engineered Products in the EU - Will the European Commission's and EMA's Action Plan on Advanced Therapy Medicinal Products make the difference?

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List of abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
ATMP	Advanced Therapy Medicinal Product
ATIMP	Advanced Therapy Investigational Medicinal Product
CAT	Committee for Advanced Therapy
CBMP	Cell-based medicinal product
CBIMP	Cell-based investigational medicinal product
CNS	Central nervous system
CAR-T	Chimeric antigen receptor T cells
EC	European Commission
EEC	European Economic Community
EMA	European Medicines Agency
ERA	Environment & Resources Authority
EU	European Union
FIH	First In Human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GSP	Good Scientific Practice
GTMP	Gene Therapy Medicinal Product
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IMP	Investigational Medicinal Product
ITEP	Investigational Tissue Engineered Product
MA	Marketing authorisation
MAA	Marketing authorisation Application / Applicant
MAH	Marketing Authorisation Holder
MCB	Master cell bank
MD	Medical Device
NCA	National Competent Authority
PEI	Paul-Ehrlich-Institute

PSUR	Periodic Safety Update Report
Q&A	Questions and Answers
QP	Qualified Person
RBA	Risk-based approach
RMP	Risk Management Plan
sCTMP	somatic Cell Therapy Medicinal Product
SME	Small and medium-sized enterprises
TCR	T-cell receptor
TEP	Tissue Engineered Product
WCB	Working cell bank

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1. Introduction

1.1 Tissue Engineered Products: Definition and Demarcation

In contrast to classic medicinal products, containing a chemical active substance, biological medicinal products are characterised by a biological active substance. This biological active substance is of biological origin or derives from biological starting material. For a long time, biological medicinal products only comprised immunological medicinal products (Art. 4, (1)), medicinal products derived from human blood or human plasma (Art. 10, (1)) and medicinal products using recombinant technologies (Annex Part A, (2)). But during the past four decades a new kind of biological medicinal products has been developed in order to treat and to prevent diseases or to restore, correct or modify physiological functions in human beings by a pharmacological, immunological or metabolic action: the Advanced Therapy Medicinal Products (ATMPs). The term ATMPs comprises three subtypes: Gene Therapy Medicinal Products (GTMPs), somatic Cell Therapy Medicinal Products (sCTMPs) and Tissue Engineered Products (TEPs) (see Fig. 1). Table 1 shows two examples of each ATMP subtype which currently have marketing authorisation (MA) in the European Union (EU).

Table 1: Exemplary overview of Advanced Therapy Medicinal Products which currently have centralised marketing authorisation in the European Union divided into the three subtypes: Tissue Engineered Products, Gene Therapy Medicinal Products and Somatic Cell Therapy Medicinal Products (own presentation).

Tissue Engineered Products			
Name	**Characteristics**	**Indication**	**Date of MA**
Holoclar	*Ex vivo* expanded autologous human corneal epithelial cells containing stem cells (3)	Treatment of adult patients with moderate to severe limbal stem cell insufficiency, unilateral or bilateral, due to burns or chemical burns of the eye (3)	17.02.2015
Spherox	Spheroids (spherical aggregates) of chondrocytes, cells of healthy cartilage, produced from the patient's own body tissue (4)	Repair of cartilage defects in the knee in patients who suffer from symptoms who suffer from symptoms (e.g. pain and problems moving the knee); used in adults and adolescents whose bones in the joints have stopped growing, when the affected area is no larger than 10 cm^2 (4)	10.07.2017

Gene Therapy Medicinal Products			
Name	**Characteristics**	**Indication**	**Date of MA**
Abecma	Is prepared using the patient's own white blood cells which are extracted from the blood and genetically modified in the laboratory (5)	Indicated for the treatment of relapsed and refractory multiple myeloma in adult patients who have received at least two prior therapies, including an immunomodulator, a proteasome inhibitor and an anti-CD38 antibody, and who have experienced disease progression during the last therapy (5)	18.08.2021
Zolgensma	Contains the active ingredient Onasemnogen-Abeparvovec, which contains genetic material from humans. It provides a fully functional copy of the SMN gene so that the body can produce sufficient SMN protein. The gene is introduced into the cells where it is needed using a modified virus (6)	Spinal muscular atrophy (SMA), a rare and serious hereditary disease which occurs when a specific gene for the production of an essential protein (the so-called survival motor neuron (SMN) protein) is missing or abnormal. The lack of SMN protein causes the nerve cells that control the muscles (motor neurons) to die off. As a result, the muscles become weak and atrophy, eventually leading to loss of the ability to move. (6)	18.05.2020
Somatic Cell Therapy Medicinal Products			
Name	**Characteristics**	**Indication**	**Date of MA**
Alofisel	Expanded human allogeneic mesenchymal adult stem cells extracted from adipose tissue (expanded adipose stem cells - eASC) (7)	Indicated for the treatment of complex perianal fistulas in adult patients with non-active/mildly active luminal Crohn's disease, when fistulas have shown an inadequate response to at least one conventional or biologic therapy. Alofisel should be used only after conditioning of the fistulas (7)	23.03.2018
Ebvallo	Allogeneic T-cell immunotherapy specific for the Epstein-Barr virus (EBV), which targets EBV-positive cells and eliminates them under HLA (human leukocyte antigen) restriction. Ebvallo is produced from T cells obtained from suitable human donors (8)	Used as monotherapy for the treatment of adult and pediatric patients from 2 years of age with relapsed or refractory Epstein-Barr virus positive post-transplant lymphoproliferative disease (EBV+ PTLD) who have received at least one prior treatment (8)	16.12.2022

Whereas two subtypes of ATMPs, the GTMPs and sCTMPs, were already clearly defined in Annex I (Part IV) to Directive 2001/83/EC, a legal definition of the third sub type, the TEPs, remained to be laid down (1). This gap was filled with the Regulation (EC) No 1394/2007/EC amending Directive 2001/83/EC, defining a TEP as 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."* (Art. 2 (1b), (9)). Cells and tissues shall be considered as "*engineered*" if they have been substantially manipulated and are (not) used for the same essential function in the recipient as in the donor (Art. 2 (1c), (9)). Furthermore, cells and tissues used for TEPs manufacturing can be of human and/or animal origin, can be viable or non-viable and may also contain additional substances, such as cellular products, bio-molecules, bio-materials, chemical substances, scaffolds or matrices (Art. 2 (1b), (9)). For that reason, many TEPs fall under the definition of combined ATMPs, consisting of a TEP component on the hand and a medical devices component on the other hand. Furthermore, products falling under the definition of TEP and sCTMP at the same time shall be considered as TEP, whereas products falling under the definition of TEP, sCTMP and GTMP shall be considered as GTMP (Art. 2 (1d (4,5)), (9)).

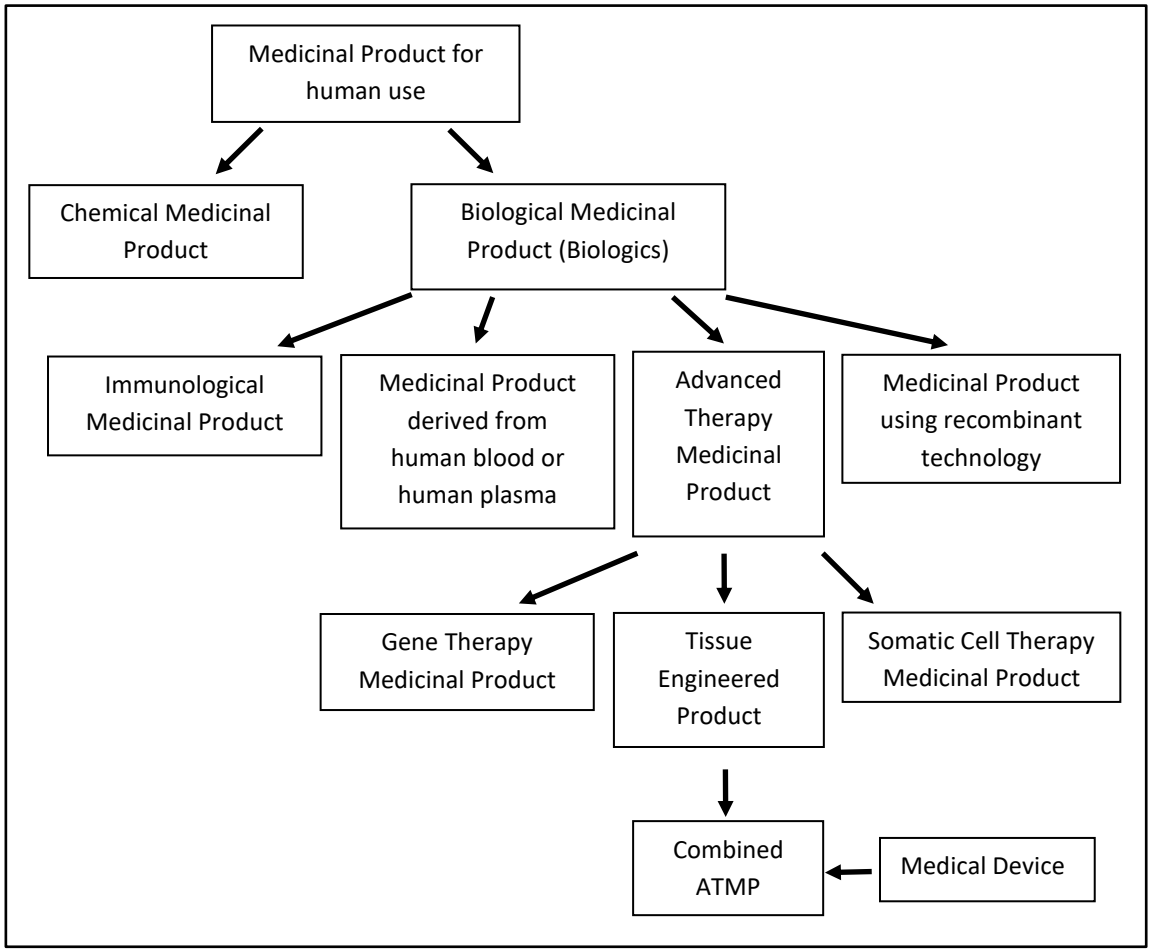

Figure 1: Systematic overview of the classification of medicinal products for human use (own depiction)

1.2 Development of Advanced Therapy Medicinal Products

Before a new medicinal product for human use gets a marketing authorisation valid in the EU, it has to go through a whole series of development steps taking ten to twelve years on average (see Fig. 2). The first step of the development process comprises basic research, including the development of new ideas to treat a certain disease or injury. The trend in ATMP development is from the one-fits-all principle towards personalised medicinal products which also consider the physiological, immunological and metabolic diversity of the human population. In the case of TEPs, personalisation is often achieved by using autologous cells as starting material.

During the second development step the production process of the new medicinal product has to be established under certain quality standards. This production process has to en-

sure an adequate and consistent product quality and safety according to Good Manufacturing Practice (GMP) standard and according to the actual stage of knowledge about the product. In contrast to the production of conventional chemical medicinal products, the production of ATMP often leads to challenges with reproducibility, comparability, traceability and stability due to their cell-based and/or personalised character. Additionally, impossible sterilisation of the active substance and the finished product containing living cells leads to the need of different requirements for the manufacturing process compared to medicinal products with a small molecule as an active substance.

In the third development phase, the preclinical testing phase, the new medicinal product is tested *in vitro* and *in vivo* regarding its pharmacological and toxicological properties according to the Good Laboratory Practice (GLP) standard. The pharmacological studies should provide a first proof of principle and should identify undesirable physiological effects of the new medicinal product. Furthermore, pharmacokinetic studies are necessary in order to investigate the resorption, distribution, metabolisation and excretion of the medicinal product. By toxicological studies a tolerable dose range and adverse effects are investigated. For *in vivo* preclinical studies suitable animal models have to be chosen. Finally, the preclinical evaluations are used to establish a risk-benefit ratio and an initial dose level for the clinical development phase. Due to the fact that ATMPs are usually not metabolised after application like conventional chemical medicinal products, several pharmacokinetic and toxicological studies according to the GLP standard are not suitable for ATMPs. For TEPs, other aspects like the immunological reaction of the recipients and local reaction of the surrounding tissue are more crucial for the risk-benefit ratio. This leads to product specific requirements for preclinical testing and a more difficult choice of suitable animal models (see chapter 3.3).

During the clinical testing phase, the new medicinal product is tested in human beings according to Good Clinical Practice (GCP) standards. The clinical testing phase usually starts with Phase I (First in Human (FIH)) clinical trials including only several healthy volunteers and providing first pharmacological, pharmacokinetic and safety data. In the case of ATMPs, it can be necessary to include patients suffering from the respective disease or condition due to major side effects or irreversibility of the therapy. Subsequently in a phase II clinical trial including up to 100-200 patients the efficacy of the IMP will become a further

parameter to be tested. In phase III clinical trials classically including up to many thousand patients, the safety and efficacy of the medicinal product will be verified. After successful phase III clinical studies, the medicinal product can obtain a marketing authorisation. Clinical studies conducted after marketing authorisation are defined as phase IV studies. They are often non-interventional and performed in order to further verify the safety and efficacy of the medicinal product under real life conditions. Due to their specific characteristics and often rare disease indications, the GCP standard is not fully suitable for ATMPs. In order to facilitate the ATMP development, requirements have to be adopted, for example, the possibility to use surrogate parameters for the proof of efficacy and safety, to use smaller study populations and to submit long-term efficacy data after marketing authorisation.

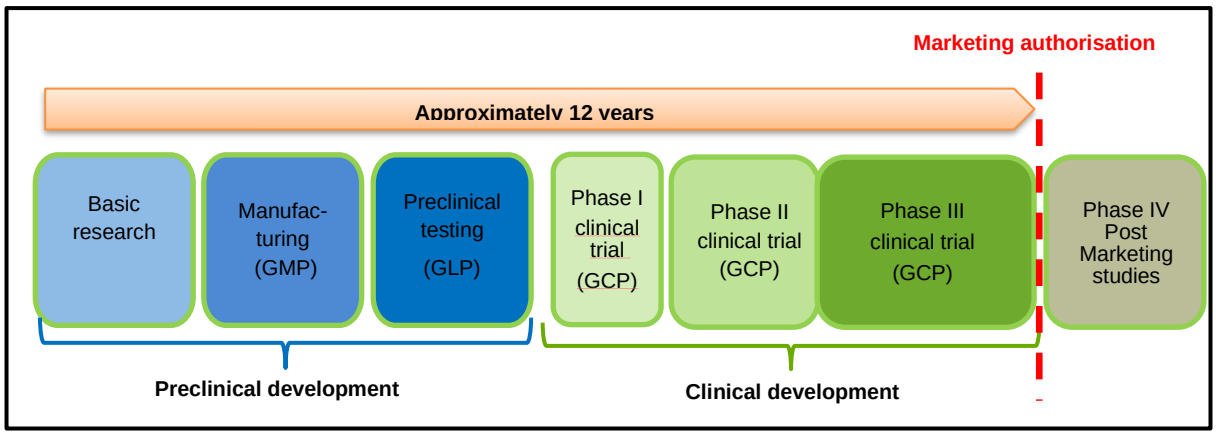

Figure 2: Overview of the development process of new medicinal products for human use (own depiction)

1.3 European legislative landscape for Tissue Engineered Medicinal Products before the European Commission's and EMA's Action Plan

This chapter provides a brief overview of the legal situation for the ATMP development in the EU prior to the action plan and summarises the most important requirements (see also table 2). More general requirements, relevant for all medicinal products for human use are not included.

1.3.1 Regulation (EC) 1394/2007 – The Lex Specialis for ATMPs

On December 30th, 2008, the Regulation (EC) 1394/2007 of the European Parliament and of the Council on Advanced Therapy Medicinal Products amending the Directive 2001/83/EC and the Regulation (EC) 726/2004 came into force and seemed to be a milestone in adaptation of the European medicinal products legislation to ATMP. Whereas the Directive 2001/83/EC defined the Community Code for marketing authorisation of all kinds of medicinal products for human use in the member states of the EU, the Regulation (EC) 1394/2007 only refers to ATMPs, excluding ATMPs which are prepared on a non-routine basis according to specific quality standards and used as a hospital exemption ((6), (9)).

The first innovation that the Regulation (EC) 1394/2007 introduced was, that the centralised authorisation procedure of medicinal products for human and veterinary use as established by the Regulation (EC) 726/2004, is also mandatory to ATMPs. Thereby, a single evaluation of quality, safety and efficacy of new ATMPs carried out to the highest possible standard by the European Medicines Agency (EMA) should be ensured and the lack of expertise in the Community should be overcome. The confidence of patients and medical professionals in the evaluation should be preserved and the market access for these innovative products should be facilitated ((9) (9)). As a further milestone, the Regulation (EC) 1394/2007 provides the first legal definition of the term "*Tissue Engineered Products (TEPs)*" and also a clear definition of the term "*engineered*", while the terms "*Gene Therapy Medicinal Products (GTMPs)*" and "*somatic Cell Therapy Medicinal Products (sCTMPs)*" already had been defined in Annex I to Directive 2001/83/EC. Additionally, ATMPs falling under the definition of more than one ATMP subtype and combined ATMPs were also defined for the first time by the Regulation (EC) 1394/2007 (Art. 2 (3-5) (9)). The Regulation (EC) 1394/2007 also determined for ATMPs containing human cells or tissues, that the donation, procurement and testing shall be made in accordance with Directive 2004/23/EC and that the rules set out in Article 6 (7) and Article 9 (4,6) of the Directive 2001/20/EC shall also be applied to TEPs (Art. 3, 4 (1) (9)). Additionally, detailed guidelines on GCP and GMP specific to ATMP were requested from the Commission, preferably within one year (Art. 4 (2), 5 (9)). In order to provide adequate specific expertise to evaluate the quality, safety and efficacy of ATMP, the establishment and the composition of a Committee for Advanced Therapy (CAT) within the European Medicines Agency was initiated by the Regulation (EC)

1394/2007 (Art. 20, 21 (9)). On the one hand, the CAT should provide support to the Committee for Medical Products for Human Use (CHMP) on any scientific assessment of the quality, safety and efficacy of ATMPs and should prepare a draft opinion for the final approval for marketing authorisation (Art. 8 (9)). On the other hand, the CAT should also provide scientific advice and recommendation on ATMP classification and development to ATMP developers with fee reductions for small and medium-sized enterprises (SME) (Art. 16, 17 (9)). Additionally, scientific evaluation and certification of quality and non-clinical data required in accordance with modules 3 and 4 of Annex I to Directive 2001/83/EC should be provided to SME requesting such support (Art. 18 (9)). As a further incentive for SME or hospitals a 50% fee reduction for marketing authorisation is introduced (Art. 19 (9)).

1.3.2 Directive 2004/23/EC Standards of quality and safety for donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

The Directive 2004/23/EC lays down standards of quality and safety for human tissues and cells intended for human applications and of manufactured products derived from human tissues and cells intended for human applications (Art.1, 2 (1) (10)). Thereby a more specific standard of quality and safety was created for ATMPs, especially for TEPs characteristically containing human tissues. The Directive 2004/23/EC has a wide range and covers all steps of handling human tissues and cells (Art. 2 (1) (10)). As the first main topic it focuses on the quality management of the tissue establishments, which have to be accredited, designated, authorised or licensed by the competent authority and have to be listed in a public accessible register (Art. 5, 10 (10)). The second main topic of the Directive 2004/23/EC is the traceability of the human tissues and cells from the donor to the recipient and vice versa including all relevant data relating to products and materials coming into contact with these tissues and cells (Art. 8 (10)). Particular specification for the different provisions are not given by the Directive 2004/23/EC, but passed on to Commission who should be supported by relevant scientific committee(s) in order to define or adapt the technical requirement to the scientific and technical progress (Art. 15-30 (10)). The notification of serious adverse events and reactions should be implemented by the member states by a system to report, investigate, register and transmit information which may influence the quality and safety of tissues and cells. How exactly the notification must be made is not specified (Art. 11

(10)). A further important point the Directive 2004/23/EC is dealing with, is the donation of tissues and cells on a strict non-profit basis, only after the informed consent or authorisation of the donor according to the national legislation of the member states and anonymously. But the criteria and technical requirements to be used for donor selection are not specifically stated (Art. 12, 13, 14 (10)).

1.3.3 Directive 2006/17/EC Technical requirements for donation, procurement, testing of human tissues and cells

Implementing Directive 2004/23/EC, Directive 2006/17/EC further develops the requirements for donation, procurement and testing of human tissues and cells by defining specification for selection criteria for donors (Annex I), laboratory tests required for donors (Annex II), laboratory tests for donors of reproductive cells (Annex III) and procurement equipment and materials (Annex IV). The Directive 2006/17/EC further specifies criteria for the exclusion of donors from donation in comparison to Directive 2004/23/EC and thereby differentiates between criteria for different donor types (Annex I (11)). A minimum set of biological tests which must be performed for all donors is also specified by the Directive 2006/17/EC as well as specific biological tests for certain donors. General requirements to be met for determining biological markers are also mentioned (Annex II (11)). One new requirement is the authorisation of qualified laboratories as testing centre by the competent authority. In comparison to Directive 2004/23/EC, Directive 2006/17/EC also specifies the tissue and/or cell donation and procurement procedure, the corresponding documentation and the packaging/labelling procedure in more detail. Finally, the reception of the tissue/cells at the tissue establishment is regulated by documented verification process (Annex IV, (11)).

1.3.4 Directive 2006/86/EC Traceability, notification of serious adverse reactions and events, technical requirements for coding, processing, preservation, storage, distribution of human tissues and cells

Implementing Directive 2004/23/EC, Directive 2006/86/EC continues and refines the requirements for the accreditation, designation, authorisation or licensing of tissue establishments (sites for processing and storage of tissues and cells) and of the tissue and cell preparation processes, the notification of serious adverse reactions and events as well as the

traceability. Additional requirements are the access to a medical registered practitioner to advise on the medical activities and the identification and minimization of risks inherent in the use and handling of biological material (Annex I (A) (12)). Furthermore, the qualification and competency of personnel is specified in more detail and has to be evaluated at appropriate intervals (Annex I (B) (12)). The obligations of Directive 2006/86/EC on equipment and materials are also more specific in comparison to Directive 2004/23/EC (Annex I (C) (12)). Additionally, detailed obligations on facilities/premises are given (Annex I (D) (12)). The second main topic in Directive 2006/86/EC are the more detailed requirements for the accreditation, designation, authorisation and licensing of tissue and cell preparation processes by the competent authority listed in Annex II (Art. 4 (12)). The third main topic of the Directive 2006/86/EC is the notification of serious adverse reactions and events. Whereas the Directive 2004/23/EC does not specify the notification process, the Directive 2006/86/EC provides a specific notification form for serious adverse reactions (Annex III) and for serious adverse events (Annex IV). Procedures to communicate to the tissue establishments and to the competent authority without delay in the case of suspected serious adverse reactions or serious adverse events should be in place (Art. 5, 6 (12)). The exchange of information between the Member States also has been driven forward by Directive 2006/86/EC by an annual report which has to be submitted by the Member States to the Commission on the notification of serious adverse reactions and events received by the competent authority (Annex V). Vice versa the Commission has to submit a summary of the reports received to the competent authorities of Member States forwarding them to the tissue establishments (Art. 7 (12)). Beyond the annual report the competent authorities should also exchange information concerning serious adverse reactions and events between each other and the Commission. Particular specifications for communication are not defined (Art. 8 (12)). A further new obligation is the single European identifying code for all donated material at the tissue establishment including specifications set out in Annex VII (Art. 10 (12)).

1.3.5 Directive 2009/120/EC - Specific technical requirements for ATMPs

The Directive 2009/120/EC emending Directive 2001/83/EC updates the specific technical requirements for marketing authorisation application for Gene Therapy Medicinal Products

(GTMPs) and somatic Cell Therapy Medicinal Products (CTMPs) and provides specific technical requirements for Tissue Engineered Products (TEPs), which were missing in Part IV of Annex I to Directive 2001/83/EC thus far, and thereby give a first orientation to TEP developers. But whereas the Directive 2009/120/EC separates between specific requirements for GTMPs, sCTMPs/TEPs and combined ATMPs, a further separation between requirements for sCTMPs and TEPs is still mostly pending. The Directive 2009/120/EC also introduces the terms "*finished product*", "*active substance*" and "*starting materials*" for ATMPs. As an important point, the Directive 2009/120/EC introduced the optional risk-based approach to determine the extent of quality, safety and efficacy data to be included in the marketing authorisation application. The risk-based approach is defined as a risk analysis covering the entire development and considering specific risk factors which are listed in detail. By the risk-based approach applicable to all ATMPs the Directive 2009/120/EC provided a flexible but justifiable approach for the TEP development. But by only defining the risk factors which may be considered for the risk analysis just a first idea on how to implement this approach was given to the developers. A further detailed description for implementation was still needed (Annex Part IV (1) (13)).

1.3.6 Guideline on human cell-based medicinal products

The multidisciplinary guideline on human cell-based medicinal products (CBMP) covers a broad range of topic areas, like the development, manufacturing and quality control as well as non-clinical and clinical development of CBMP, including sCTMP and TEPs. Non-viable cells and cellular fragments originating from human cells and xenogeneic cell-based medicinal products are excluded from the scope. The guideline is relevant for products entering the Marketing Authorisation (MA) procedure, but also investigational medicinal products entering into clinical trials (Art. 1 (14)). It seems to be an important basis for Directive 2009/120/EC. The guideline mentions the optional risk-based approach for the development plans and evaluation requirements of CBMP and provides a list of general risk criteria (Art. 4.1 (14)). Concerning quality and manufacturing aspects the guideline provides requirements for starting and raw materials, the manufacturing process, characterisation of the CBMP, quality control, validation of the manufacturing process, development pharmaceutics, traceability and comparability are further specified in detail (Art. 4.2 (14)). Concerning the pre-clinical testing of CBMP points to the risk-based approach, due to the fact

that conventional requirements for pharmacological and toxicological testing of medicinal products may not always be appropriate for CBMP. Furthermore, important CBMP specific points to consider in non-clinical studies are discussed (Art. 4.3 (14)). Due to the specific biologic characteristics of CBMP, alternative approaches to Phase I to Phase III clinical trials are discussed as well. Beside a strong recommendation of an "*European scientific advice*", CBMP specific study design are discussed and specification for a safety database in order to detect common adverse events are provided (Art. 4.4 (14)).

1.3.7 Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products

After the risk-based approach was first introduced by the Directive 2009/120/EC amending Annex I, part IV of Directive 2001/82/EC, a more detailed methodology of this optional and highly flexible approach and clear definitions for the terms "*risk-based approach*", "*risk*", "*risk factors*" and "*risk profiling*" were provided by the "*Guideline on risk-based approach according to annex I, Part IV of Directive 2001/83/EC*" applied to ATMPs. The Guideline emphasises that the risk-based approach profiles each risk inherent to the product from the beginning of product development to the submission of the Marketing Authorisation Application (MAA) on an on-going basis. The identified risk profile should be used to justify the extent of quality, non-clinical and clinical data in the MAA. The methodology of the risk profiling is defined and explained in four steps. Examples for risk profiling of different products are given (15).

1.3.8 Guideline on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medicinal Products

This Guideline was published in order to meet the request of Article 14 (4) of Regulation (EC) No 1394/2007 concerning detailed guidance on the post-authorisation follow-up of safety and efficacy as well as risk management of ATMPs. The specific rules described in this guideline are set up in addition to the common rules for post-authorisation surveillance (pharmacovigilance) of medicinal products for human use (Art. 5 (16)). Firstly, the guideline provides a list of possible risks which should help the developers to make further considerations about their ATMP. The listed risks are related to all steps during the development

process from product manufacturing, handling, application and clinical follow-up and include more common risks as well as ATMP specific risks. The guideline highlights the importance of post-authorisation efficacy follow-up for ATMP because a full efficacy assessment of ATMPs can need up to several years (Art. 6.2 (16)). Guidance concerning the design of clinical follow-up studies with ATMPs is also provided based on the experience so far but does not replace the scientific advice (Art 6.3 (16)). Furthermore, requirements for the pharmacovigilance system of Marketing Authorisation Holders (MAH) referring to the Article 14(1) of the Regulation (EC) No 1394/2007 and additional requirements for the risk management system are mentioned in detail (Art. 7, 8 (16)). The guideline further introduces different regulatory tools for the management of post-authorisation commitments for ATMPs. These tools for products authorised via centralised procedure include letters of commitments, follow-up measures, conditional approvals or approvals under exceptional circumstances with specific obligations and their annual re-assessments with corresponding reporting obligations (Art. 9 (16)). Special needs for the electronic exchange of the pharmacovigilance data of ATMPs in EudraVigilance system were recognized and adaptions are planned (Art. 10 (16)). Pharmacovigilance inspections, including risk management plan and benefit-risk review by the EMA are introduced in order to ensure compliance monitoring (Art. 11 (16)). In the end the guideline provides the requirements concerning the personal data protection while using follow-up systems, risk minimisation plans and traceability systems. Important points to follow are to strictly limit the data access to the staff that are obliged by professional secrecy and to use the data only for the purpose it was collected (Art. 12 (16)).

1.3.9 EudraLex Volume 4 Annex 2 Manufacturing of Biological active substances and Medicinal Products for Human Use

Before its revision in 2018 resulting in the exclusion of ATMPs, Annex 2 to the Eudralex Volume 4 EU guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use was the full range of biological active substances and medicinal products for human use. Therefore, the guidance on manufacture was not very specific to ATMP, especially to TEPs, but provided a more common overview of the special requirements on biological medicinal product production. It is divided into two parts: Part A, deal-

ing with general guidance on the whole manufacturing process of biological active substances and medicinal products and Part B, dealing with specific guidance on selected product types, including the chapter "*Somatic and xenogeneic cell therapy products and tissue engineered products*". The chapter describes some specific requirements concerning combined products, control and test measures to avoid contamination and infections, aseptical manufacturing, documented procedures for the secure handling and storage of products, sterility tests and a stability-monitoring program.

Table 2: Overview of the European legislative landscape relevant for ATMPs before the EC's and EMA's Action Plan (own compilation)

Legislation	**Innovation**
Regulation (EC) 1394/2007	Central Marketing Authorisation Procedure mandatory for ATMPs
	Clear definition of the term "*TEP*", "*Engineered*", "*Combined ATMPs*"
	Request for ATMP specific GCP, GMP, post authorisation follow-up and risk management guidelines
	Establishment of CAT
	Incentives for SME: scientific evaluation and certification, fee reduction
Directive 2004/23/EC	Request for Community standards and specifications for activities relating to the quality system
	Traceability of the human tissues and cells from the donor to the recipient and vice versa
	Public register of tissue establishments
	Warning system for quality and safety of tissues and cells
	Informed consent or authorisation of the donor
Directive 2006/17/EC	Specifications of donor selection criteria for the tissue and/or cell donation and procurement procedure, the corresponding documentation and the packaging/labelling procedure in more detail
	Authorisation of qualified laboratories as testing centre by the competent authority
	Reception of the tissue/cells at the tissue establishment is regulated by documented verification process.
Directive 2006/86/EC	Continued and refined requirements for the accreditation, designation, authorisation or licensing of tissue establishments and of the tissue and cell preparation process
	Notification form for SAE and SAR, records and procedures to communicate with the competent authorities
	Annual report form to inform all Member States
	European identifying code for all donated material at the tissue establishment
Directive 2009/120/EC	Specific technical requirements for ATMP; Definition of the terms "*finished product*", "*active substance*" and "*starting materials*" for ATMP
	Introduction of the optional risk-based approach, but no detailed description for implementation
Guideline on human cell-based medicinal products	Requirements for starting and raw materials, the manufacturing process, characterisation of the CBMP, quality control, validation of the manufacturing process, development pharmaceutics, traceability and comparability are further specified in detail
	CBMP specific points to consider in non-clinical studies

	CBMP specific clinical study design are discussed and specification for a safety database are provided
Guideline on the RBA applied to ATMPs	More detailed methodology of the optional RBA in four steps, including examples
	Clear definitions for the terms "*RBA*", "*risk*", "*risk factors*" and "*risk profiling*"
Guideline on Safety and Efficacy Follow-up – Risk Management of ATMPs	Risks related to all steps during the development process of ATMPs
	Highlights the importance of a post-authorisation efficacy follow-up for ATMP over long time periods and guidance on clinical follow-up study design
	Requirements for the pharmacovigilance system
	Additional requirements for the risk management of ATMPs
	Introduction of different regulatory tools for the management of post-authorisation commitments for ATMPs
	Special needs for the electronic exchange of the pharmacovigilance data of ATMPs in EudraVigilance system were recognized
	Pharmacovigilance inspections
	Personal data protection
EudraLex Volume 4 Annex 2 (before revision in 2018)	Specific guidance on manufacturing of biological medicinal products, including ATMPs.

1.4 Issues in ATMP development

Although ATMPs are developed since approximately forty years, currently only 18 have got a marketing authorisation (MA) valid in the European Union (EU) (see examples in table 1). Two of them are TEPs, Spherox (Spheroids from autologous chondrocytes) and Holoclar (Living cornea tissue equivalent) (17). Out of this, the following questions arise: Why is the number of ATMPs, especially TEPs, with granted marketing authorisation so small? And what can be done to improve the ATMP development and to facilitate marketing authorisation? To answer this questions, different points have to be considered. While ATMPs offer great clinical perspectives for unmet medical needs and rare diseases, like spinal muscular atrophy (SMA), most EU-approved products have not achieved satisfactory commercial success. Due to the high variability and instability of biological active substances and the highly personalised nature, the development and the manufacturing of ATMPs is usually associated with high costs, stringent regulatory requirements and complex interventional procedures (18). On the one hand, a common legislation for all biologicals, including ATMPs, is hardly possible, but must be individually adapted to the respective characteristics and associated requirements. On the other hand, ATMP developers need concrete orientation concerning standards manufacturing, non-clinical and clinical trial design, especially because ATMPs often are developed in an academic environment or by small and medium-sized enterprises which miss regulatory expertise and capital. All the more, developer and manufacturer of ATMPs need ATMP specific and detailed guidance documents for successful development, marketing authorisation application and life cycle management of new innovative ATMPs, especially TEPs.

In order to identify the key issues in ATMP development, the EMA hosted a workshop for stakeholders with diverse backgrounds in May 2016. Representatives from academia, industry, pharmacists, physicians, patients, consortia, incubators, investors, health technology assessment (HTA) bodies, EU regulators and the European Commission were present. The main topics discussed were: Facilitating research and development, optimising regulatory processes for ATMPs, moving from hospital exemption to marketing authorisation and improving funding, investment and patient access. The outcome of the workshop was published by the EMA in June 2016 by the document "*Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe*".

In the field "*Facilitating research and development*", ATMP manufacturing was identified as one of the main challenges of developers due to many related issues like homogeneity of cell starting material, maintaining continuous supply of raw materials, unsuitable manufacturing requirements for all ATMPs, complexity of upgrading immature developmental production, technologies to commercial manufacture, process validation and product characterisation. In the preclinical and clinical development stages, finding relevant animal models, clinical study design, a lack of regulatory knowledge and insufficient financial support and incentives were identified as main challenges (Art. 2 (19)). One major stakeholders proposal was for licensing requirements considering the unique particularities of ATMP manufacture, for example, ATMP manufacture at various sites, including sites close to the bedside at hospitals. Furthermore, more flexible requirements during early developmental phases were requested by the stakeholders, especially for cell-based products, including low-risk (non-substantially manipulated) products, and the process validation requirements for many ATMPs. Another major topic were the different requirements among the member states for genetically modified organisms (GMOs) and the resulting challenging integration of GMO assessment in (multicenter) clinical trials authorisation. Therefore, harmonisation was requested by the stakeholders. Harmonisation was also requested for the requirements for cells and tissues used as starting materials, for excipients and raw materials used for the manufacture process. Consideration also should be given to novel development tools (e.g. organoids, extrapolation, modelling/simulation, biomarkers, etc.). A further identified challenge was the difficult benefit-risk assessment of ATMPs, which also has to consider the expected but realistic benefits, particularly where patients have incurable diseases or where suitable treatments are lacking. More guidance with the risk-based approach was also requested, especially for the Qualified Persons (QPs). Additionally, a careful consideration of benefit-risk balance during early development stages supported by an informal dialogue with the Innovation Task Force (ITF) network and a more formal discussion through scientific advice with the CAT was proposed as well. In general, the stakeholders called for more regulatory support for academic spin-offs and SMEs, including better training for stakeholder groups and the creation of a dedicated EMA office for academia with expertise in ATMPs.

The second topic "*Optimising regulatory processes for ATMPs*" revealed the stakeholders proposal for a more streamlined interaction with the EMA and associated committees during the ATMP classification procedure, the certification procedure, scientific advice or early access

schemes like PRIME or adaptive pathways. The stakeholders also ask for a certification procedure, including not only preclinical aspects and allowing also non-SMEs, in particular academia and spin-off incubators, as well as to larger companies. Another problem mentioned by the stakeholders was the missing uniformity on how regulatory requirements, including classification, apply in different member states. Therefore, an overview of national requirements for GMOs and tissue and cell and blood products is needed before a greater harmonisation can occur. The stakeholders also asked for international harmonisation, for example through ICH, in order to enhance international research and to improve the regulation of exchanging starting or intermediate materials as well as final licensing of products. Regulators are also asked to challenge the existing principles of comparability and orphan similarity in order to adapt them on ATMPs and develop specific guidance and training, in the context of both standard and decentralised manufacturing of ATMPs, new active status and changes to the active substance. Furthermore, the developers highlighted the question of process versus product and proposed to consider ATMPs more from a process point of a view, especially at the early phases of development. Disease registries were also proposed in order to monitor safety and help companies collect structured data and meet pharmacovigilance and post-authorisation requirements.

For the third topic "*From hospital exemption to marketing authorisation*" the stakeholders suggested a more uniform implementation of the hospital exemption across the member states. Additionally, it was asked for a better public availability of detailed hospital exemptions products in all Member States and systematic collection of clinical safety and efficacy data in order to facilitate the path to marketing authorisation. Other requested actions were more support with regulatory, manufacturing and pharmacovigilance activities. Finally, the restriction of hospital exemption to the area of high unmet medical need where no ATMP is licensed was considered, in order to minimise competition between licensed medicinal products and hospital exemption products and incentivise the development of therapies with demonstrated quality and clinical benefit (Art. 4 (19)).

For the fourth topic "*Funding, investment and market access*" the stakeholders suggested a higher awareness of financial incentives by the regulators, provision of early EMA/HTA advice and an EU-wide infrastructure for specialised centres to improve efficiency and quality of care. Additionally, regulators were asked to foster collaboration between private investors and the

EC (IMI, Horizon 2020) to provide continuity and complementary funding and to fund registries to support comparative evaluation and post-marketing data collection. HTAs and payers were requested to engage earlier in development process, to provide platform for informal dialogue, to issue ATMP guidance and increase uptake of parallel advice and to coordinate actions in relation to reimbursement. Finally, funding based on realistic patient benefit with multi-stakeholder input and monitoring, including regulatory, GMP and manufacturing costs was proposed by the stakeholders (Art. 5 (19)).

1.5 Aim of this thesis

The aim of this thesis is to provide firstly a comparison of the European legislative landscape concerning ATMPs, especially TEPs, before and six years after the Commission's and EMA's Action Plan on ATMPs has been published. In addition, it is assessed which points of the action plan have already been implemented and whether the previously identified stakeholders' issues have been sufficiently addressed. Therefore, the new or revised (draft) guidelines relevant for TEPs are critically reviewed, still existing regulatory gaps are revealed and recommendations are given .

2. Comparison of the stakeholders' proposals and the proposed actions published in the EC's and EMA's Action Plan

Based on the issues identified by the EMA's ATMP stakeholders workshop in 2016, the Commission (Directorate General Health and Food Safety) and the EMA published an Action Plan on ATMPs in October 2017 in order to initiate certain follow-up actions to improve and to facilitate the development and the marketing authorisation of innovative new ATMP in the EU (20). Additionally, in 2018, 2020 and 2023 the CAT published Work Plans presenting planned activities including timelines and responsible committee participants. The proposed actions target challenges identified at all stages of development. On the one hand, the action plan includes several services and activities like an enhanced scientific support for the ATMP developers, an increased support and training of all stakeholders and an improved communication between the stakeholders and the competent authorities. On the other hand, it includes guidance documents specific on ATMPs, like new guidelines, revisions of existing guidelines and Q&A documents (20), (21). All issues identified by the ATMP stakeholders relevant for regulators are listed in table 3 and allocated to the corresponding proposed actions of the EC's and EMA's Action Plan on ATMPs and to the already implemented actions. Additionally, the current status of the proposed action (09/2023) was checked and is indicated by a colour code. Actions and guidance documents which are already completed are marked in green, actions which are still ongoing are marked in yellow and actions which are still pending are marked in red. It must be considered, that the categorisation of the action status does not evaluate the quality of the action. The quality of the new guidance documents or revisions are checked and discussed in chapter 3 of this thesis.

Table 3: Comparison of the issues identified by stakeholders at EMA's ATMP workshop on 27 May 2016, the proposed actions of the EC's and EMA's Action Plan on ATMPs and implemented actions with current status: Guideline completed ■ ongoing ■ pending ■ (own presentation)

** further discussed in chapter 3*

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
Research and development			
1	Apply GMP more flexibly in early development phases	EC Guideline on GMP for ATMPs	"*Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" (05/2018)*
2	Increase transparency of manufacturing authorisation requirements across Europe / Facilitate to share of national experience of ATMP GMP inspections	Exchange of information on GMP inspections within the network	• GMDP Inspector's Working Group • Compilation of Union Procedures on Inspections and exchange of Information (last update 06/2023)
3	Promote innovative manufacturing technologies (e.g. bedside manufacturing / closed systems)		"*Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" (05/2018)*
4	Promote innovative manufacturing models (e.g. decentralised manufacturing)		"*Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" (05/2018)*

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
5	Promote a master file system for excipients and raw materials used in the production of ATMP		"*Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" (05/2018)*
6	Encourage development of manufacturing sites, as a service		
7	Align GMO assessment with clinical trial applications as currently done for marketing authorisation applications	EC's initiation of a dialogue with national competent authorities to address the interplay between GMO and the medicines legislation	EMA's SOP "*Consultation of environmental competent authorities on genetically modified organisms with respect to environmental risk assessment for medicinal products for human use*" (12/2019)
8	Set up central GMO repository listing the requirements and timelines for GMO assessment		Repository of national requirements and other agreed actions (published in EC's website)
9	Harmonise Member State implementation of GMO Directive		Guidance document "*Good Practice on the assessment of GMO-related aspects in the context of clinical trials with human cells genetically modified 1 – Version 5*" (11/2021)

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
10	Create public database for EU cell and tissue authorities and approved establishments as a resource for stakeholders		EC platform available – EU Tissue and Cell Product Compendium
11	Harmonise EU-wide requirements for cells, tissues and blood used as starting materials for ATMPs		"*Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" (05/2018)*
12	Rethink risk-based approach, placing additional emphasis on expected benefits	EMA Q&A on the application of the risk-based approach for ATMPs that have not been subject to substantial manipulation	Q&A on the application of the risk-based approach for ATMPs that have not been subject to substantial manipulation (07/2017)
13	Set up dedicated EMA office for academia with expertise in ATMPs		
14	Increase incentives and regulatory support	Increased stakeholder support - Academia	• Academia Collaboration Matrix Action Plan (04/2021) • EMA pilot with guidance through regulatory process and fee reductions and waivers (09/2022)

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
			• Training materials and webinars ADVANCED EU training project in cooperation with EATRIS
15	Provide more ATMP specific guidance (e.g. on comparability)	Provide enhanced scientific support for the development of ATMPs; EMA Scientific Guidelines on ATMPs: GLP for ATMPs	No guideline, only Q&A document on GLP principles relevant for ATMPs (01/2017)
		Revision of the "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products*"	Draft of "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products – Revision 1*" (02/2018)*
		Revision of the draft "*Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products*"	Revised draft "*Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products*" (07/2018)
		GCP for ATMPs	"*Guidelines on Good Clinical Practice specific to ATMPs*" (10/2019)*

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
		New guideline on comparability for cell-based MPs	No guideline, only Q&A document on "*Comparability considerations for ATMPs*" (12/2019)
		Scientific considerations on gene editing technologies	Expert group meeting on genome editing technologies used in medicinal product development (10/2017)
		Revision of "*Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*" including scientific considerations on gene editing technologies	"*Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells - Revision 1*" (11/2020)*
		Increased stakeholder support – ATMP topic-specific	EMA webpage has been updated, support for advanced therapy developers
16	Promote novel development tools (organoids, extrapolation, modelling/simulation, biomarkers)		"*Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials*"

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
Optimising the regulatory process			
17	Streamline EMA internal regulatory processes for ATMPs	Revision of EMA procedures regarding the assessment of ATMPs	Revised guidance concerning Procedural Advice on the Evaluation of ATMPs (01/2018)*
18	Promote use of early access tools (PRIME, adaptive pathways, ITF, scientific advice, certification and HTA parallel advice) / Provide ATMP specific workshops and trainings	Increased stakeholder support - SME	• PRIME: priority medicines program • Action Plan for SMEs (05/2017) • SME User guide • Briefing meetings with EMA • Translation assistance for product information • Guidance on clinical data publication • SME news letters • Training events
19	Consider opening certification to non-SMEs and strengthen its value		
20	Coordination of sharing relevant information from scientific advice letters and certification applications		Q&A documents on: • Exemption from batch controls carried out on ATMPs imported into the EU from a third country (07/2019)

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
			• Use of out-of-specification batches of authorised cell/tissue-based ATMPs (04/2019) • Principles of GMP for the manufacturing of starting materials of biological origin used to transfer genetic material for the manufacturing of ATMPs (02/2021)
21	Publish overview of national requirements (for GMOs and tissue, cell and blood products) and move towards greater uniformity		Repository of national requirements has been published in the EC's website
22	Harmonise application documents (e.g. CTAs and scientific advice applications)		Clinical Trial Information System (CTIS) since 01/2023 for all initial clinical trial applications in the EU
23	Harmonise global requirements (with US and Japan, through ICH)		
24	Guideline on investigational medicinal products and comparability	EMA Guideline on Investigational ATMPs	Draft "*Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials*" (02/2019)*

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
25	Adapt concept of orphan similarity to ATMPs		Q&A related to the assessment of similarity for ATMPs in the context of the orphan legislation (latest update 04/2021)
26	Promote disease registries to collect structured data on efficacy and safety (publish list of registries, harmonise data standards, promote use of electronic medical records)		"*Guideline on registry-based studies*" (10/2021)*
Moving from hospital exemption to marketing authorisation			
27	Implement hospital exemption more uniformly across Member States	The EC services to initiate a reflection process with the Member States on the hospital exemption	
28	Make details of hospital exemption products in each Member State publicly available		
29	Collect clinical data and experience systematically		

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
30	Provide support with manufacturing and pharmacovigilance activities		
31	Consider restricting hospital exemption to areas of high unmet medical need where no ATMP is licensed		
Funding, investment and market access			
32	For Regulators: Raise awareness of financial incentives		• 65% fee reduction for a request for scientific advice for ATMPs (90% for SMEs); • 90% fee reduction for the certification procedure
33	Provide vehicle for SMEs and academia to seek early parallel EMA/HTA advice	Interaction with EUnetHTA	• Collaboration in the frame of the EMA-EunetHTA 2017-2020 Work Plan (11/2017) • Report on the implementation of the EMA-EUnetHTA work plan 2017 – 2021 (06/2021) • Priority topics for European collaboration between regulators and health technology assessment bodies - Development of a joint

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
			work plan (2021-2023) between EMA and European HTA bodies facilitated through EUnetHTA21 (04/2022)
34	Support and develop EU-wide infrastructure for specialised centres to improve efficiency and quality of care		
35	Foster collaboration between private investors and EC (IMI, Horizon 2020) to provide continuity and complementary funding	Increase awareness of stakeholders on EU regulatory processes and framework	• EMA participation to EHC Round Table on Economics and Access, Healthcare, System and Novel Therapies (02/2018) • DIA conferences (04/2018), (05/2018), (06/2018) • TOPRA Symposium – Stockholm, Sweden (10/2018) • CAT meeting with interested parties (09/2018) • EMA/CAT Regulatory session at the ESGCT 2018 congress (10/2018)

	Main stakeholders' proposals identified by EMA's stakeholders workshop (19)	**Proposed Actions published in the EC's and EMA's Action Plan** (20)	**Actions and their current status (09/2023)**
36	Fund registries to support comparative evaluation and post-marketing data collection		EMA has set up a cross-committee task force on registries and published "*Patient Registry Initiative- Strategy and Mandate of the Cross-Committee Task Force*" (05/2017)
37	Coordinated training and information sharing on specific scientific and regulatory matters within the network	Awareness and training of the network	CAT ad-hoc expert meetings and workshops: • Expert meeting on scientific and regulatory considerations for adeno-associated viral vector (AVV)-based gene therapy (9/2017) • Chimeric antigen receptor (CAR) T cell therapy registries workshop (02/2018)

3 New guidance for the development of Tissue Engineered Products

This chapter focusses on the quality assessment of the new guidance documents and revisions which are most relevant for TEP development (marked by a * in table 3). Thereby, the documents are also compared to the previous versions or guidance documents. Available draft versions are also considered.

3.1 EudraLex Volume 4 Part IV - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products

According to the demand of Article 5 of Regulation (EC) No 1394/2007 in 2008, ATMP specific GMP guidelines were actually only developed and published by the European Commission in 2017. As Article 63 (1) of Regulation (EU) No 536/2014, supplemented by the Regulation (EU) 2017/1569, requested GMP guidance also for investigational medicinal products, the described GMP requirements are applicable to the manufacturing of authorised ATMPs and to investigational ATMPs. Even ATMPs administered to patients as hospital exemption have to be manufactured under equivalent quality standards (Art. 1.10-1.12 (22)). In this chapter, the Guidelines on GMP specific to ATMPs are compared to the Eudralex Volume 4 Annex 2, previously also valid for ATMP. The GMP Guidelines specific for ATMPs start with the definition of the Pharmaceutical Quality System and the obligation to install it for ATMP manufacturer in order to ensure compliance with GMP requirements (Art. 1.2, 1.25, 1.26 (22)). Due to the fact, that the Pharmaceutical Quality System was already introduced by the ICH Q10 guideline and is originally based on the International Standards Organisation (ISO) 9000 quality standards, this is no new requirements for ATMP manufacturer introduced by the guidelines. Especially because the scope of ICH Q10 already includes biological products as well as investigational products and thereby is also relevant for ATMPs (Art. 1.1, 1.2 (23)).

The next aspect of the GMP guidelines is the introduction of the risk-based approach as an alternative approach for manufacturing applicable to all types of ATMP (Art. 1.15, 2.13, 2.23, 2.25 (22)). Thereby the risk-based approach is defined and the possibility to use an informal risk management process is introduced on the condition that the level of effort and documentation is commensurate with the level of risk (Art. 2.18 (22)). As a result, the risk-based approach brings a high flexibility and can facilitate compliance with GMP but also brings a high self-responsibility for the manufacturer, who are responsible for the quality of the ATMPs they

produce (Art. 2.14, 2.15, 2.16 (22)). Examples for the risk-based approach in conjunction with raw materials, the testing strategy, ATMPs that are not subject to substantial manipulation and investigational ATMPs are given. Alternative testing strategies for sterility tests to the finished product, particulate matter tests or on-going stability programs for products with shorter shelf life are acceptable. For investigational medicinal products in very early phase/proof of concept trials, it may be exceptionally possible to manufacture the product in an open system (when the product is exposed to the environment, e.g. working under laminar air flow) and a critical clean area under certain conditions. The level of formality and detail for the documentation can be adapted to the stage of development and during early phases of clinical development (clinical trial phases I and I/II) specifications can be based on wider acceptance criteria (Art. 2.3.1-2.3.4 (22)). After the risk-based approach was firstly introduced by the "*Directive 2009/120/EC amending Annex I, part IV of Directive 2001/83/EC*", a more detailed methodology as well as several fictitious examples for GTMP, sCTMP and TEPs were provided by the "*Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to ATMPs*" (Art. 4, Annex I-III (15)). Therefore, the concept of the risk-based approach is not new, but is discussed in more detail and applied to different aspects of the manufacturing process by the guidelines. Important exceptions, particularly in relation to early development phases, are mentioned, which could accelerate and simplify development. The necessary exceptions are granted and particular examples are given, which developers can use as a guide. This is an important step forward. However, it is questionable whether this will be applicable to every ATMP, as the diversity is so great. In addition, the wording of the exceptions is sometimes vague which in turn could cause problems in interpretation.

Furthermore, the guidelines provide additional and more detailed requirements for the qualifications, practical experience and training of the personal involved in manufacturing or testing of the ATMP in comparison to the Eudralex Volume 4 Annex 2. The training requirements include a successful process simulation test, a system of disqualification of personnel, periodical assessment of the effectiveness of training and records of training. Also, the separation of quality assurance and production as well as the clear definition and assignment of key roles by the senior management are new requirement introduced by the "*GMP guidelines specific to ATMPs*" (Art. 3.1, 3.2, 3.4 (22)). Concerning the hygiene of manufacturing process clear rules on clothing, behavior and insurance of health conditions of the personnel are provided (Art. 3.3 (22)). In comparison to Eudralex Volume 4 Annex 2, the new GMP Guidelines provide

a detailed four step process in order to qualify premises and equipment for the production of ATMPs based on a documented risk assessment (Art. 10 (22)). For investigational ATMPs the minimum requirements like the suitability of the air quality system and of the premises has to be verified. Critical aspects of the premises and the equipment with regard to the specific risks of the intended manufacturing process have to be qualified as well. Re-qualification has to be considered if a new type of ATMP should be manufactured in an already qualified premises (Art. 10.1.1 (22)). The qualification process includes the four steps: (1) setting of user requirement specifications, (2) design qualification, (3) verifying compliance with the user requirements specification (Installation Qualification, Operational Qualification and Performance Qualification) and (4) documentation (Art. 10.1.2 (22)). Furthermore, cleaning procedures, the manufacturing process, test methods and transport conditions have to be validated to gain documented evidence that it can consistently produce a result within the specific parameters (Art. 10.2-10.5 (22)). Thereby, the GMP guidelines specific for ATMPs provide much more specific and systematic instructions concerning the personnel, the premises and the equipment for the manufacturing of ATMPs and thereby create a safer framework for production. This predefined framework is essential, especially for less experienced universities and SME. Clear specifications are the prerequisite for getting a correct implementation and creation of a GMP-compliant environment.

The guidelines also define the documentation for the manufacturing much more detailed and differentiates two types of documentation: *"Specifications and instructions"* and *"Records and Reports"* (Art. 6.1 (22)). In order to ensure compliance with the MA/CTA specifications for materials, the finished product and the manufacturing instruction have to be defined. The minimum requirements for documentation of specification of raw materials, starting materials, intermediate and bulk products and primary packaging, batch definition, manufacturing instructions and specifications for finished product are provided (Art. 6.2 (22)). In the case of investigational ATMPs adaptions according to the product type and the stage of development are accepted for the product specification file and if necessary, the system used to ensure the blinding has to be described and verified (Art. 6.3 (22)). Thereby, the documentation is more clearly structured and more concrete orientation is given to the manufacturer. This could help to simplify and accelerate the development of a new product, especially in the initial phase. Furthermore, the minimum requirements for the records and reports are set out in order to

confirm the compliance with specifications and instructions and to be the basis for certification, batch release and traceability. Additional documentation has to be performed for several procedures, like for example, the qualification of the premises and equipment as well as for the validation of the manufacturing process. A site master file has to be prepared for every site involved in the manufacturing of authorised ATMP and the retention period for the batch documentation is specified as well. (Art. 6.4, 6.5 (22)). This takes into account that ATMPs are often manufactured in several locations and thus facilitates proof of GMP compliance. In the case of documentation of traceability in order to track cells/tissues contained in ATMPs from the donator to the recipient and vice versa, the guidelines do not provide any new specifications and refer to Article 15 of the Regulation 1394/2007 and thereby indirectly to Directive 2004/23/EC and Directive 2002/98/EC (Art. 6.6 (22)).

Concerning raw materials the guidelines take into account that in some cases raw materials are only available in research grade instead of pharmaceutical grade. Conditions for use are the understanding and mitigation of related risks and the assurance of the suitability for the intended use is. The consideration of this special feature also simplifies the development and manufacturing of new ATMPs. In general, the ATMP manufacturer have to verify the compliance of the supplier's materials with the agreed specifications and the risk of viral and microbial contamination of raw materials of biological origin during their passage along the supply chain must be assessed. Specific labeling requirements for stored raw materials, release by a person responsible for quality control and full traceability are necessary (Art. 7.2 (22)).

For the donation, procurement and testing of human tissues and cells used as starting materials the guidelines are largely consistent with the Eudralex Volume 4 Annex 2 and also refer to the Directive 2004/23/EC and for blood-derived cells to Directive 2002/98/EC. The accreditation, designation, authorisation or licensing of the supplier of starting materials have to be verified by the ATMP manufacturer. Additionally, the ATMP manufacturer have to establish specifications for the starting materials which should be agreed with the supplier(s) and compliance has the be verified. Depending on the product's characteristics, additional testing may be required. Also clear provisions about the transfer of information regarding the starting materials have to be in place. The risk of contamination for the starting materials during their passage along the supply chain must be assessed, have to be released by the person responsible for quality control and have to be labeled adequately while storage. Like already the

Eudralex Volume 4 Annex 2, the guidelines take into account that in some cases the results from the test(s) required to release the starting materials take a long time and therefore the starting materials have to be released before the results of the test(s) are available. The risk, for example, a product contamination should be clearly assessed and understood. In such cases, the finished product should only be released if the results of these tests are satisfactory, unless appropriate risk mitigation measures are implemented. Different from the Eudralex Volume 4 Annex 2, the guidelines grant the new exemption that the manufacture of an ATMP starts from already available cells or tissues where some initial processing/manufacturing steps have been performed outside of the GMP environment. This scenario is only possible if such material cannot be replaced with GMP-compliant material and if a risk analysis is performed to identify the testing requirements necessary to ensure the quality of the starting material. The overall responsibility for the quality lies with the ATMP manufacturer (and/or, as appropriate, the sponsor or marketing authorisation holder) and the release of such cells/tissues for use in the manufacturing process should be done by the person responsible for quality control. Additionally, the competent authorities should agree to the control strategy. Specific requirements for xenogeneic cell and tissues are also provided (Art. 7.3 (22)). Thereby, the guidelines address the specific needs of ATMP manufacturers and provide more flexibility for the manufacturing process.

Concerning the use of master and working seed lots/cell banks for allogeneic products, the guidelines largely comply with the Eudralex Volume 4 Annex 2 but further specify compliance with GMP. Cell bank safety testing and characterisation are specified for batch-to-batch consistency, control measures for the storage and quarantine and release procedures should be followed. In the case of investigational ATMPs, a gradual approach is acceptable (Art. 8 (22)). Also concerning the production operations, the guidelines provide exceptions concerning investigational ATMPs and requirements for new manufacturing formula or manufacturing processes (Art. 9.1 (22)). The guidelines also provide specific requirements for the handling of incoming materials and products, including receipt and quarantine, sampling, storage, labelling and packaging as well as for utilizes, including water, medical gases and clean stream (Art. 9.2, 9.3 (22)). Measures to prevent cross-contamination appropriate to the risks identified are additionally listed in detail (Art. 9.4 (22)). Because of the fact, that the majority of ATMPs cannot be terminally sterilized, the guidelines mention requirements for an aseptic manufactur-

ing process. Thereby, different requirements are provided for the production in closed systems, in open systems and for the production by using further technologies. Once again exceptions for investigational ATMPs are granted as well. The validation of the aseptic processing is also described, including a simulation test. Also, the sterilisation process(es) applied have to be suitable for the specific product characteristics and should be validated as well. Alternative methods for solutions and liquids, that cannot be sterilised are additionally described (Art. 9.5 (22)). Thereby, the guidelines provide more options and flexibility in sterilisation und its validation specific to ATMPs in comparison to the Eudralex Volume 4 Annex 2. Modern methods and possibilities are considered and described in concrete terms. Thereby, more orientation for ATMP manufacture is available. Exemptions for investigational ATMPs are considered again in order to facilitate and accelerate ATMP development.

Further operational principles, like the monitoring of critical quality parameters as identified in the marketing authorisation/clinical trial authorisation (e.g. identity, purity, biological activity, potency and stability), environmental controls and control strategy when using chromatography equipment, are considered as well by the guidelines (Art. 9.6 (22)). The requirements for primary packaging materials and the corresponding documentation are specified more detailed and adapted to the phase of development in comparison to Eudralex Volume 4 Annex 2. Special requirements are provided for the labelling of investigational ATMPs, for re-packaging and re-labelling operations and the blinding system (Art. 9.7 (22)). Furthermore, requirements for finished products are provided, including quarantine until their release and the exceptional release of products before completion of all quality control tests as well as appropriate measures to prevent mix-ups of autologous products and other dedicated products (Art. 9.8 (22)). As a new additional point, requirements for rejected materials are mentioned, including the option of reprocessing of rejected authorized and investigational products under certain circumstances (Art. 9.9 (22)). Thereby, ATMP-specific challenges such as the high production costs and the scarcity of starting materials are considered and the manufacturer get the possibility to use materials for production more carefully and sparingly and by this to better safeguard ongoing manufacturing of ATMPs.

In comparison to the Eudralex Volume 4 Annex 2, the guidelines specify the qualification, the responsibilities and tasks of the Qualified Person (QP) in more detail. The guidelines set the requirement that each ATMP manufacturing site must have at least one Qualified Person who

has to verify, certify and release every batch of ATMPs for sale, marketing authorisation or clinical trial. The requirements for the three steps of the batch release process are also provided in detail, including adaptions to investigational ATMPs. In exceptional cases and due to the short shelf life of some ATMPs, the batch release can be performed already before the results of quality control tests are available. Requirements for this special process are provided. As an ATMP typical issue, the decentralised manufacturing of ATMPs is also considered in this context. Special considerations are taken into account and specific additional requirements are provided, including for example, the identification of a "*central site*" to review and monitor the further manufacturing sites (Art. 11.2, 11.3 (22)). The guidelines also bring flexibility for the handling of unplanned deviations in manufacturing process and the administration of out of specification products. On the one hand ATMPs can be certified and released, if the products still meet the specifications although unplanned deviations in the manufacturing process did occur. One the other hand, in exceptional cases the administration of out of specification products can be acceptable to avoid an immediate significant hazard to the patient and if requested by the treating physician. The sponsor and the relevant competent authority have to be informed by the manufacturer in such cases (Art. 11.4, 11.5 (22)). These are very important adaptations to the needs of ATMP manufacturers and patients who rely on the ATMPs. Due to the exemptions supply bottlenecks and failures can be mitigated.

The guidelines also describe the quality control (QC) more detailed, especially the sampling of raw materials, active substances, intermediate products, primary packaging materials, fully packed units as well as testing and on-going stability programs (Art. 12 (22)). In contrast to Eudralex Volume 4 Annex 2, requirements for outsourced activities are provided, including obligations for the contract giver and the contract acceptor (Art. 13 (22)). Additionally, the handling of quality defects and product recalls is described in detail. Central points of the system which should be put in place are the independent recording and investigation from marketing and sales departments, the timely information of the QP and the competent authorities, the assessment of the risk(s) posed by the quality defect and the need for appropriate corrective or preventive measures, the assessment of the impact of any recall action and the internal and external communications that should be made. An unblinding procedure for investigational ATMPs in the case of prompt recalls has to be established by manufacturer as well (Art. 14 (22)). This ensures faster processing of quality defects and increases patient safety.

In contrast to Eudralex Volume 4 Annex 2, the guidelines specify a risk assessment for ATMP containing or consisting of GMOs which should result in a categorisation of the product in one of four different risk levels for the environment. According to the risk level, containment measures and emergency plans have to be established (Art. 15 (22)). Due to the fact, that the requirements for GMOs differ among the Member States and therefore the integration of GMO assessment in multicenter clinical trials is a major challenge in ATMP development, the guidelines take up an important topic in this regard. The guidelines provide a new differentiation of ATMP containing GMO by four different risk levels according to the results of the risk assessment. This enables a more flexible way of working for ATMP manufacturer and reduces the workload during development, especially for products with a low risk level. But on the other hand, no specific requirements are assigned to the individual risk levels, what still leaves room for interpretation. It therefore remains to be seen whether these requirements are sufficient for harmonisation.

The guidelines also address the possibility that reconstitution of products after batch release can be performed at the administration site outside a GMP environment, if it is necessary and does not contain any substantial manipulation. A detailed and clear description of the reconstitution activities has to be provided. In case of authorised ATMPs, the manufacturer has to validate the reconstitution process from batch release to administration through appropriate studies (Art. 16 (22)). At least, the guidelines provide requirements for an automated production of ATMPs, including the qualification of the equipment, SOPs, adequate maintenance, validated aseptic processing, batch and traceability reports and batch certification (Art. 17 (22)). Thereby, two new issues are addressed by the guidelines in comparison to Eudralex Volume 4 Annex 2. On the one hand, it is taken into account that many ATMPs are administered at special centres and close to bed site by the possibility to reconstitute products after batch release at the administration site outside a GMP environment is provided. On the other hand, new technologies like the automated production of ATMPs is also included in the considerations and offers the developers appropriate orientation.

3.2 Draft Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products – Revision 1

As already requested by Article 14 (4) of Regulation (EC) No 1394/2007, the "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products*" was firstly set up by the EMA in 2008 in on order to provide specific requirements for ATMPs concerning the post-authorisation follow-up of efficacy and safety. The guideline offers specific guidance on the pharmacovigilance system, the identification of risks and corresponding minimisation measures, post-authorisation safety and efficacy studies, the management and reporting of adverse reactions and of the evaluation of the effectiveness of the risk management system (see also chapter 1.3.8). The first revision of the guideline which is still ongoing since 2018 should update all main sections based on experience gained from the marketing authorisation applications received. In this chapter, the first revision is compared to the previous version of the "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products*".

Firstly, the guideline provides more detailed guidance on the safety and efficacy aspects which have to be considered in the risk management plan to be agreed as part of the marketing authorisation by giving examples for different kind of risks related to patients or others and corresponding safety specifications (Art. 5.1, 5.2 (24)). Although a list of risks to patients already existed in the previous version of the guideline, the examples are updated concerning new technologies like using embryonic stem cells, induced pluripotent stem cells, mesenchymal stem cells and CAR T cells. But nevertheless, the examples are merely a checklist and starting point for the manufacturers, helping them with the identification of risks and the transfer to their own product. Many of the risks were already discussed in the previous version of the guideline and/or in the Guideline on human cell-based medicinal products (Art. 4.2 (14)). Additionally, the guideline provides ATMP specific considerations concerning pharmacovigilance activities, like procedures for follow-up of reported adverse reactions which allows identification of the batch and the use of patients' data collected for regulatory purposes (Art. 6 (24)). Thereby, no new aspects are raised concerning TEPs. The advice to use traceability data for surveillance purposes was already given in the previous version of the guideline.

Furthermore, the guideline provides suggestions concerning risk minimization measures. Thereby, a concept of using only selected accredited centres for ATMP administration and

involving only adequately trained and experienced physicians is proposed, including a detailed description of an education program for different target groups (Art. 7.2 (24)). Additionally, specific tools to measure the effectiveness of risk minimisation are provided (Art. 7.3 (24)). While the concept of using only accredited centres and appropriately trained personnel for the application of ATMPs is already mentioned in the previous version of the guideline, the level of detail and the specificity of the proposed training material increases in the current revision. But no new proposals are made to verify the effectiveness of the measures.

In comparison to the previous version of the guideline, the revision provides more detailed considerations on efficacy and safety follow-up of ATMPs. Because of highly limited efficacy data available at the time of the marketing authorisation in many cases, several years of follow-up are necessary to gain a comprehensive understanding on the long-term efficacy of ATMPs. The guideline clarifies, that safety and efficacy follow-up is generally required for all recipients of an ATMP. If the follow-up should be limited to a defined subset of patients, scientific justification has to be provided. The duration of the safety and efficacy follow-up has to be established on a case by case basis. Thereby, reasons for discontinuation of therapy or discontinuation of follow-up, and re-administration or re-initiation of therapy should be of particular interest for long term efficacy follow-up. For the design of safety and efficacy studies usual clinical practice should be used for follow-up whenever possible and a comparative design should be preferred. The use of existing databases or disease registries as a data source is introduced as one option to permit longer-term follow-up (Art. 8.2, 8.3 (24)). Thereby, the stakeholders' request to use of patient registries in order to gain post marketing safety and efficacy data is addressed for the first time. Additionally, objectives for long-term safety follow-up of different kinds of ATMPs are provided by the guideline, including cell based products and combined products. Concerning the study design, duration and study population some current examples has been added in the revision, including new technologies, but no further aspects are discussed.

ATMP specific considerations are also provided concerning the management and the reporting of adverse reactions and periodic safety update reports. Thereby, the signal detection and monitoring in order to identify new risks and any changes in existing risks are central points (Art. 9 (24)). Finally, requirements for compliance monitoring by the marketing authorisation

holder and the competent authorities are specified, which were already mentioned in the previous version, including the reporting route and consequences in the case of non-compliance from the EMA to the European Commission (Art. 10 (24)).

3.3 European Commission's Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products

The Regulation (EC) No 1394/2007 already requested GCP guidance specific to ATMPs and the design of clinical trial with ATMPs was identified as one of the biggest challenges in ATMP development. Issues like a lack of suitable animal models, a low patient number due to rare disease indication, little disease progression knowledge, problems with the creation and interpretation of endpoints for new indications and a lack of study personnel with ATMP-specific knowledge were found and confirmed that more flexible requirements are needed for ATMP development ((25), (26), (27)). Therefore, the European Commission published Guidelines on Good Clinical Practice specific to ATMPs in 2019. Nevertheless, the Regulation (EU) No 536/2014 and the general ICH GCP Guideline E6 (R2) are still true for clinical trials with ATMPs as well (Art. 1.1, 1.2 (28)). The new GCP guidelines specific to ATMPs are divided into ten chapters which are discussed below and partly compared to the "*Guideline on human cell-based medicinal products*".

The first topic which is discussed in the new GCP guidelines specific for ATMPs is the clinical trials design. Concerning the study population, examples of particular ATMP specific considerations related to the benefits risk ratio for the subjects are given (Art. 2 (i) (28)). Thereby, the stakeholders' issue "*difficult benefit-risk assessment of ATMPs*" is taken into account. But instead of focusing on the expected but realistic benefits, ATMP-specific risks are listed which does not really address the actual concerns of the stakeholders. Concerning the cohort size, the guidelines grant more flexibility by pointing out that for determining the disease prevalence and manufacturing capacity must be considered. Furthermore, the guidelines provide ATMP-specific recommendations for the clinical study design, for example, if no active comparator is available or appropriately justified (Art. 2 (ii), (iii), (iv), (v) (28)). The challenge on defining a dose range for early phase clinical trials is mentioned and ATMP specific issues which have to be considered are listed. High flexibility for the dose range and repeatability is granted with respect to the specific characteristics of ATMPs and examples are given. Also, the option of dose definition based on published literature data is described (Art. 2 (vi) (28)).

On the one hand, the guidelines refer to the issues to find suitable animal models and a low patient number due to rare disease indication, by providing alternative ways to specify the dose range for early phase clinical trials and the cohort size and list particular considerations for the study population. This could help to define more specific inclusion and exclusion criteria for the study population and thereby reduce drop outs and enhance the quality of clinical data. Flexibility is also provided concerning the study design. But on the other hand, one of the most important challenges in ATMP development - the difficult subject recruitment due to rare disease indication – is not further specified. Unfortunately, no particular strategies, tools or resources to achieve a more efficient subject recruitment are provided.

The guidelines also point to the challenges in pre-clinical studies. Key topics are to find suitable animal models in order to provide reliable safety information and problems to conduct traditional non-clinical pharmacokinetic (PK) or dose finding studies (Art. 3 (28)). Therefore, alternative approaches in order to define a dose range in phase I (First in Human) studies are discussed, providing the needed flexibility to the ATMP developers. But a clear structured step by step guidance is pending. Especially in the academic and SME setting, where missing regulatory expertise and missing practical experience complicate the clinical development, more specific support would be appropriate. For example, clear advice like a decision tree for the study design and appropriate statistical models for the dose finding could provide the needed orientation.

Concerning the quality of investigational ATMPs, the guidelines cross-refer to the new "*Guidelines on Good Manufacturing Practice for ATMPs*" as they are also relevant for investigational ATMPs. Additionally, the often complex use and storage of investigational ATMPs with often a short shelf life is taken into account, resulting in very detailed instructions and information that have to be provided to the clinical trial site, additional necessary documentation about the time from manufacture to administration and adequate training of investigators, especially, if reconstitution of the investigational ATMP is necessary (Art. 4.1, 4.4 (28)). The guidelines also refer to IMPDs for ATMPs containing cells or tissues of human origin or medical devices. Beside a confirmation of compliance with Directive 2004/23/EC or Directive 2002/98/EC, IMPDs for ATMPs containing cells or tissues of human origin need a confirmation to have a traceability system for bidirectional tracking of cells/tissues in place (Art. 4.2 (28)). Medical devices which are used as part of the active substance or the formulation ("*combined*

ATMP") have to be considered in the IMPD as well, including information on the characteristics, performance and intended use of the device and on compliance with the relevant general safety and performance requirements provided by the Regulation (EU) No 2017/745 on medical devices. Thereby, the ATMP developers get an overview of additional regulatory requirements in the case of using cells/tissues of human origin or medical devices as part of the ATMP. But a proposed strategy to optimally coordinate and streamline the requirements and conformation certificates is missing. Due to the fact that especially CBMP specific guidelines usually are implemented in different ways across the Member States this would be a critical aspect.

The lack of study personnel with ATMP-specific knowledge is picked up at various points in the guidelines. In this chapter it is specified that the sponsor should provide adequate instructions and training on complex handling processes and reconstitution of investigational ATMPs (Art. 4.1, 4.4 (28)). It remains to be seen whether this kind of training is sufficient or whether improved education concepts concerning clinical trials with ATMP on a more general level and with documented evidence (e.g. certificates) and regular refresher are needed.

In order to enhance the safe conduct of clinical trials with ATMPs, the guidelines specify that the IB additionally should provide comprehensive information on the risks of the product, including risks associated with the administration procedure and/or upstream interventions, information on short and long-term safety issues, information on the potential impact of previous or concomitant treatments or treatment failure and highlight the consent of the clinical trial subjects (Art. 5.1, 9 (28)). The level of information should be in relation to the risks and if necessary, information on risk minimisation measures should also be provided in the Protocol and the IB (Art. 5.2, 5.3 (28)). In general, these are not new provisions, as the IB already had to contain all information regarding the risks concerning the medicinal product itself and its application according to the ICH GCP E6 (R2). To describe the necessary information in detail is certainly helpful for the developers, but it is not a new requirement.

Additionally, the guidelines require a clear explanation and where appropriate, training about the upstream interventions on subjects and administration procedures, if they deviate from standard clinical practice (Art. 6.1 (28)). In justified exemptions the presence of the sponsor during the administration of the investigational ATMP to the clinical trial subject or in any upstream collection procedure is acceptable and has to be explained in the informed consent (Art. 6.2 (28)). The additional information on risks in the IB, the additional training about the

upstream interventions on subjects and administration procedures as well as a more detailed education of clinical trial subjects could help to enhance the competence of clinical trial professionals and to improve the quality of the clinical data.

The guidelines also highlight the importance of traceability in clinical trials with ATMP and therefore specify a system to trace each investigational ATMP from delivery to the clinical trial site up to the administration to the clinical trial subject. Additionally, for investigational products containing cells or tissues of human origin, the traceability from the recipient to the donor of the cells or tissues has to be ensured and vice versa. Due to the protection of personal data an anonymous coding system has to be used (Art. 7 (28)). In the field of traceability in clinical trials with ATMPs, the guidelines do not bring additional guidance compared to previous guidelines. The traceability of IMPDs containing cell/tissue of human origin from donor to recipient and during the whole clinical trials was already specified by the "*Guideline on human cell-based medicinal products*" which also includes investigational products.

Furthermore, the guidelines figure out, that the maintenance of investigational product(s) used in the trials to reconfirm specifications, can be challenging in the case of ATMPs due to the scarcity of the materials. Therefore, it is possible to justify not to retain samples of the investigational ATMP in case of autologous ATMPs and certain allogeneic ATMPs. The retention period should be adjusted to the stability and shelf life of the product (Art. 8 (28)). Because already the "*Guideline on human cell-based medicinal products*" set the requirement to retain samples "*whenever possible*" (Art. 4.2.4 (14)) it seems to be not an completely new ATMP specific requirement providing more flexibility to ATMP developer.

In general, the guidelines have a strong focus on safety and protection of clinical trial subjects. The comprehensive information on the expected benefits and risks of the product, including risks associated with the administration procedure and/or upstream interventions on subjects, information on short and long-term safety issues and the consent of the clinical trial subjects are highlighted (Art. 9 (28)). Additionally, the guidelines deal with the exemption of unmet release specifications in case of necessary administration of the cell/tissue based ATMP to avoid an immediate significant hazard to the subject. In this case, the supply of the product to the investigator is justified after the investigator's request and the evaluation of the risks (Art. 9.3 (28)). Thereby, the guidelines provide a new exemption specific to investigational

ATMPs and create further flexibility for the clinical development, possibly resulting in more positive study outcomes and an accelerated development process.

Concerning the safety reporting, the guidelines promote a differentiated causality assessment for each component of the ATMP, the application process and, where applicable, any required concomitant medication. In cases where long-term follow-up of trial subjects is necessary, the reporting of adverse events during the follow-up period should be clearly separated from the study period (Art. 10 (28)). Concerning the monitoring of clinical trials with ATMPs containing cells or tissues of human origin the guidelines specify that it should also cover compliance with the traceability requirements and the compliance with the arrangements for long-term follow-up (Art. 11 (28)). The requirements for safety reporting and monitoring set by the guidelines seem to be a logical consequence of previous requirements instead of complete new requirements improving the flexibility in early phase development of ATMPs.

3.4 Guideline "*Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*" Revision 1

Because genetically modified cells can be used as starting material for manufacturing of tissue engineering products, the first revision of the guideline "*Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*" is also relevant for TEP developers. The revision was realized in order to include the recent developments and the latest technologies in the area of genetically modified cells (Art. 1,2 (29)). In this chapter, the revision is discussed and compared to the previous version of the Guideline "*Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*".

In the first revision of the Guideline "*Quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*", the quality section has been updated to include the evolution of science and regulatory experience on starting materials and genome editing reagents/tools, comparability and validation. Beside the risk-based approach for the design of the manufacturing process, specific aspects which should be addressed for the process validation are provided and the case of limited availability of the cells/tissues is discussed by the guideline. The option of a reduced process validation, if necessary, is described under the condition of additional in-process testing to demonstrate consistency of production. If storage of intermediates occurs, it is also necessary to validate the storage conditions and

transport, where applicable (Art. 4.2.5 (29)). Additionally, the guideline specifies what the demonstration of comparability does exactly mean and that it can be sufficient if products are highly comparable before and after changes. Furthermore, examples of the regulatory expectations with regards to comparability studies are given (Art. 4.2.6 (29)). Characterisation and identification of Critical Quality Attributes which typically include those properties or characteristics that affect identity, purity, biological activity, potency and stability, and are important for the drug substance/drug product manufacturing process is especially essential. The characterisation studies which should be addressed are listed (Art. 4.3 (29)). These characteristics are also relevant as release criteria. In case release testing cannot be performed on the actual product, either a surrogate product sample should be tested or analyses should be performed with key intermediates. In exceptional and well justified cases, a two-step release testing program may be carried out. In such cases, the missing information at first-step release should be compensated by an appropriate in process testing and a more extensive process validation as outlined above. In process testing normally includes testing of critical raw materials, starting materials, active substance/intermediates/finished products, and stability testing. In case product material is too limited for full release testing, a reduced program could be justified on a risk-based approach tailored to the individual product specificities (Art. 4 4 (29)). While the option of a reduced process validation was already introduced by the "*GMP guidelines specific for ATMPs*", the two-step release program is a new exemption that gives the developers further flexibility.

The non-clinical section has been updated with current thinking on the requirements to conduct non-clinical studies, including studies required to assess the proof-of-concept and biodistribution of the product, to identify potential target organs of toxicity, and to obtain information on dose selection for clinical trials, to support the route of administration and dosing schedule (Art. 5 (29)). Additionally, the guideline includes a specific section on the scientific principles and guidance for CAR-T cell and TCR products, induced pluripotent stem cell derived cell-based products and cell-based products derived from genome editing (Art. 5.3 (29)).

The clinical section has been updated considering the experience of recent scientific advices and MAAs. Additionally, an Annex on clinical aspects specific to CAR-T cells has been included. The clinical section addresses the requirements for studying pharmacological properties of the cell itself and the transgene. The requirements for efficacy studies emphasise that the

same principles apply as for the clinical development of any other medicinal product, especially those of current guidelines relating to specific therapeutic areas. The clinical section further addresses the safety evaluation of the product as well as the principles for follow up and the pharmacovigilance requirements (Art. 6 (29)). The non-clinical and clinical section has also been adapted to the current state of the art and offer some examples that are also relevant for TEP manufacturers. New considerations adapted to the latest technical developments are presented here. This can support the manufacturer in developing non-clinical and clinical concepts as well as ensuring regulatory compliance. Especially the sections concerning induced pluripotent stem cell derived cell-based products and cell-based products derived from genome editing can be also relevant to TEP developers.

3.5 Updated guidance document "*Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007*"

The ATMP specific evaluation procedure for marketing authorisation applications was firstly described in Article 8 of the Regulation 1394/2007. Thereby, the main structures of the cooperation between the Committee for Medicinal Products for Human Use (CHMP) and the Committee on Advanced Therapies (CAT) were already described, but the regulation also called for a specific procedure for the evaluation of marketing authorisation application. Therefore, a first draft of the guidance document "*Procedural advice on the evaluation of ATMPs in accordance with Article 8 of Regulation (EC) No 1394/2007*" was published in 2009 and concentrated on the initial evaluation of new ATMPs. However, its principles can also be applied to post-authorisation procedures. After the EC's and EMA's ATMP stakeholders workshop an update of the draft guidance document was initiated and is available since 2018. The aim of the update was to clarify the evaluation procedure and to help developers to navigate through the regulatory process in the EU. In this chapter, the updated guidance document is discussed and compared to the previous version.

The draft of the updated guidance document firstly describes the composition of the assessment teams and appointment of rapporteurs. Beside the CAT and CHMP, the Pharmacovigilance Risk Assessment Committee (PRAC), established in 2012, is additionally introduced as a further scientific committee (Art. 4 (30)). In the next step, the roles and responsibilities of all interested parties involved in the evaluation procedure are described more detailed and timelines for the interactions between the applicants, EMA and its committees are revised (Art. 5,

6 (30)). The new timelines do not contain major changes, except an additional option of extending the clock stops in justified cases. Thereby, developers have more time to respond to questions raised by the Committees. Furthermore, the updated guidance document streamlines the processes for adopting the lists of questions and issues by the committees and clarifies in which situations an oral explanation might be needed (Art. 6 (30)).

By the update of the guidance document the stakeholders' request for revision of the guidance document "*Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007*". Thereby, the understanding of the evaluation process by specifying the roles and procedure more detailed in comparison to the previous version is facilitated. Additionally, procedural aspects were streamlined and the possibility to extend the clock stops in justified cases are new advantages for the ATMP developers and could facilitate and accelerate the application process.

3.6 Draft Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials

More flexible requirements during the early developmental phases of ATMPs were a major request of stakeholders interviewed in the Commission's and EMA's workshop (see chapter 1.4). This refers to more individual, product- and risk-specific requirements. The draft version of the "*Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials*" takes up this request and focus on more flexible requirements for investigational ATMPs (ATIMPs), especially for early exploratory trials, in contrast to authorised ATMPs. In this chapter, the draft version of the "*Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials*" is discussed and compared to the "*GMP guidelines specific to ATMPs*" and the "*GCP guidelines specific to ATMPs*".

The multidisciplinary guideline provides guidance on the structure and data requirements for a clinical trial application and should help the ATMPs developers to design their development program, unless they are also encouraged to seek early advice at the competent authorities. Thereby, the guideline differentiates between exploratory and confirmatory trials. The risk-based approach forms the basis for determining the content of the IMPD (Art. 1,2 (31)). In the first section the guideline specifies the documentation concerning the quality of the ATIMP.

Thereby, data requirements evolve as the development progresses from exploratory to confirmatory clinical trials. Only for the conduct of confirmatory clinical trials a mature manufacturing process and specifications that match with the marketing authorisation are expected. Furthermore, the guideline describes different regulatory scenarios for combined products. On the one hand, flexibility is provided for quality data requirements, especially in the early development phase. But on the other hand, the evolving data requirements are no new simplification for the developers in general, because the "*GMP guidelines specific to ATMPs*" which are also relevant for ATIMPs already grant adaptions concerning the documentation for ATIMPs in the product specification file according to the product type and the stage of development (Art. 6.3 (22)). Also, the regulatory scenarios for combined products are not fundamentally new requirements, as they were already included in the "*GCP guidelines specific to ATMPs*" (Art. 4.3 (28)). Therefore, the new guideline does not grant additional flexibility concerning the quality of ATMPs in early development phases.

The quality documentation is further specified in detail and is divided into two parts: documentation for the active substance and documentation for the investigational medicinal product. The needed data about the manufacturing process and process controls for the active substance are specified firstly. As an adaption to ATIMPs in early phase development, it is accepted that the in process controls focus on the minimum safety aspects according to the actual knowledge, although critical steps should be already identified and adequate acceptance criteria should be established. The documentation of starting materials and raw materials used for the manufacturing process of the active substance are also specified. Thereby, it is acknowledged that, in some cases, only raw materials of research grade are available. In this case, it is accepted that to use raw materials of research grade if the risks are understood. Furthermore, it is accepted, that working cell banks for CBMP may not be established prior to phase I trials and that initial manufacturing steps might not have been conducted under full GMP compliance (Art. S.2.3 (31)). Critical steps in the manufacturing process should be identified as appropriate for the stage of development and all available data and acceptance criteria should be provided. It must be considered, that due to limited data at an early stage of development complete information may not be available (Art. S.2.4 (31)). The manufacturing process for ATIMPs is not expected to be validated for early clinical trials. But to ensure compliance with the requirements in the clinical trial authorisation, appropriate monitoring and

control measures should be implemented. Only for confirmatory clinical trials process validation is required (Art. S.2.5 (31)). Thereby, the guideline considers, that manufacturing processes and their control strategies are continuously being improved and optimized, especially during early phases of clinical trials. As a requirement, these changes need to be adequately documented and evaluated through the whole development. Comparability testing in the case of exploratory clinical trials is generally not expected to be as extensive as for approved products. Whereas during the confirmatory clinical studies changes to the manufacturing process and the final product should be avoided (Art. S.2.6 (31)). The flexibility, that the manufacturing process for investigational ATMPs is not expected to be validated, was already introduced by the GMP guidelines specific to ATMP, except for aseptic processes (Art. 10.3 (22)). The same is true for the option to improve and optimize the manufacturing process and control strategies during the early development phase (Art. 10.4 (22)). Therefore, there is no further flexibility introduced for the manufacturer at this point either.

The guideline also specifies characterisation studies, resulting in a comprehensive knowledge of the ATIMP and appropriate control of quality parameters related to efficacy and safety prior to first in human clinical trials (Art. S.3.1 (31)). During early phases of clinical development specification can include wider acceptance criteria based on the current knowledge of the risks (Art. S.4.1 (31)). The validation of analytical procedures is also understood as an evolving process (Art. S.4.2, S.4.3 (31)). For exploratory clinical trials results from relevant non-clinical and test batches should be provided. In confirmatory trials, data from all batches produced should normally be provided (Art. S.4.4 (31)). A justification for the quality attributes which may be relevant to the performance of the medicinal product is required already for an exploratory clinical study. It is acknowledged that during early clinical development when there is only limited experience, the acceptance criteria may be wide (Art. S.4.5 (31)). For ATIMPs it is recommended to establish a reference batch as soon as possible and immediate packaging material used for the active substance should be stated and a description of the container closure system should also be provided (Art. S.5, S.6 (31)). Additionally, a stability protocol of the active substance is needed. In the case of IMPs based on autologous cells, it is acceptable to use early stability evaluations on results with cells from healthy donors due to ethical considerations. For gene therapy IMP, vector integrity, biological activity (including transduction capacity) and strength are critical product attributes which should always be included in stability studies. Furthermore, where feasible forced degradation studies may also be performed

in order to provide important information on degradation products and to identify stability indicating parameters to be tested. Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. For confirmatory clinical trials a clear stability profile and the claimed shelf life of the active substance should be provided (Art. S.7 (31)). Furthermore, the guideline provides the documentation requirements for the ATIMP which are largely the same as the requirements for the active substance. Additional requirements are the description of composition and the pharmaceutical development, including steps like cryopreservation or reconstitution. For confirmatory clinical trials the reconstitution process is expected to be validated. The maximum acceptable bioburden prior to the filtration must be provided and aseptic processes have to be validated. Reprocessing may be acceptable for particular manufacturing steps if adequately described and appropriately justified (Art. P1-3 (31)). Furthermore, information on the excipients, including their qualification for their combination with cells should be provided. Established excipients should preferably be of pharmaceutical grade, but in exceptional cases also non-pharmaceutical grade materials can be used. For excipients of human or animal origin, information has to be provided regarding adventitious agents' safety evaluation and viral safety data (Art. P4 (31)). In case of limited amount of final product, it is possible to rely on intermediate product release criteria. If it necessary to release the drug product batch prior to all results of specification testing is available, this needs to be justified and supported by performed risk analysis and a procedure for out of specification test results need to be described (Art. P5 (31)). Additionally, a risk assessment with respect to potential contamination with adventitious agents of human or animal origin should be provided (Art. A2 (31)). The "*GMP guidelines specific to ATMPs*" already accepted a gradual approach of validation of the test methods for ATIMPs. Only for pivotal clinical trials validation of analytical methods for batch release and stability testing is expected. The only exemption are sterility and microbial assays and assays to ensure patient's safety (Art. 10.4 (22)). Additionally, the option of batch release prior to obtaining the results of quality control test was introduced by the "*GMP guidelines specific to ATMPs*" (Art. 11.3.2 (22)). But the possibility to use non-pharmaceutical grade excipients in exceptional cases, is not explicit mentioned in the GMP guidelines. The same is true for the possibility to rely on intermediate product release criteria in the case of limited amount of final product. At that point, the guideline provides a greater flexibility for ATMP developer.

For the non-clinical data documentation, the guideline also grants potential flexibility. Again, the risk-based approach should be used to identify the necessary non-clinical data on a case-by-case basis. Furthermore, ATMP specific recommendations are given concerning the study design, including route of administration and application procedure, dose levels tested and animal models used (Art. 5.1 (31)). It is mentioned, that for ATIMPs, standard toxicity studies with healthy animals are not always appropriate and that disease models can provide clinically meaningful safety data instead. The need for toxicity studies should be determined on a case by case basis. Furthermore, recommendation for choosing the right animal model for toxicology investigations and the pharmacokinetic studies are given. The development and use of cell- and tissue-based models including 2D and 3D tissue-models, organoids and microfluidics, are encouraged, especially for evaluating the mode of action (Art. 5.2 (31)). Additionally, ATMP specific recommendations for pharmacology studies are provided, including proof-of-concept studies and pharmacokinetic studies (Art. 5.3 (31)). Safety/toxicity studies may not be needed if adequate safety endpoints are included in proof of concept studies and in justified cases *in vitro* and/or *ex vivo* data can be used. As a further exceptional condition, it is recognised that, due to the specific characteristics of ATMPs, it would not always be possible to conduct these studies in full conformity with GLP (Art. 5.4 (31)). At least, a minimum set of non-clinical data requirements before first-in-human studies are provided by the guideline. The extent of the non-clinical data package as a whole is determined on a case-by-case basis by a risk assessment (Art. 5.5 (31)). Also, non-clinical data that can be provided at later stages of development, including long term safety data, are provided by the guideline (Art. 5.6 (31)). Non-clinical data for combined ATMPs, including the data concerning the device component alone are described (Art. 5.7 (31)). The guideline thus enables the developer to adapt the requirements to the characteristics of the product without working strictly according to the specifications of GLP. By ATIMP specific recommendations concerning the study design, including route of administration and application procedure, dose levels tested and animal models used, the guideline also supports the manufacturer in his decision-making process.

The guideline mentions, that especially in the early clinical phase characteristics and features of ATMPs are expected to have an impact on the trial design. Further points which are special for clinical trials with ATMPs are the benefit-risk-assessment and the choice of the trial population. In order to support ATMP developers, anticipated benefits and risks for trial subjects are listed and considerations when choosing a trial population are provided (Art. 6.1 (31)). The

guideline also considers, that the design of exploratory trials of ATIMPs often involves consideration of clinical safety issues different from other medicinal products. For example, extended or permanent adverse effects, long-term or delayed safety issues. Especially, the design of FIH clinical trials with ATIMPs deserves specific considerations, because the extrapolation from non-clinical pharmacodynamic, pharmacokinetic/biodistribution and toxicity data to the human situation may be limited. Therefore, the prediction of a safe starting dose for FIH trials and the prediction of target organs of toxicity may be much more difficult. Furthermore, the guideline provides ATMP specific safety and tolerability objectives. It specifies the sources for determining the ATIMP dose to be administered, including non-clinical studies with the product, data of related products and literature data. Additionally, factors to consider in the risk assessment of ATIMPs are mentioned as well, including the risk of the therapeutic procedure as a whole, biological processes and medical devices which are used. Because differences between animals and humans may limit the predictive value of non-clinical dose-finding studies, the guideline provides ATIMP specific aspects to consider for selecting dose, schedule and enrolment. Pharmacokinetic assessment should be conducted where feasible. Specific pharmacodynamic objectives for ATIMPs are mentioned (Art. 6.2 (31)). For confirmatory clinical trials recommendations for the study design are provided. Especially, alternatives are discussed if no reference or comparator treatment is available and if usual blinding methods are not practicable. Also, for efficacy studies ATIMP specific considerations are discussed. For example, additional co-primary or secondary cell- and tissue-specific endpoints may be required for investigational TEP and a long-term follow-up is necessary, if the efficacy is dependent on the long-term persistence of the product. The detection of the risks should continue during confirmatory clinical trials and should enable the developer to predict the safety profile of the ATMP (Art. 6.3 (31)). In some cases also long term efficacy and safety data could be necessary. Follow-up of patients should be more intensive in first two years after treatment at minimum (Art. 6.4 (31)). Thereby, the guideline also address two important issue, identified by the stakeholders workshop: benefit-risk-assessment and study design specific for ATMPs. Flexibility and ATMP specific examples are provided in both fields in order to support the developers. Additionally, TEP specific examples are given. Although, many points are also taken up in the GCP guideline specific to ATMPs, they are continued in more detail. This makes it easier for the developers to take specific ATMP difficulties into account when planning clinical trials.

3.7 Guideline on registry-based studies

The use of patient registries in order to collect post-marketing clinical data was one of the ATMP developer's request which was revealed in the stakeholders workshop. The draft of the "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products – Revision 1*" already took up the topic in 2018 by providing specifications on the use of registries during the safety and efficacy follow-up. Additionally, the EMA Patient Registry Initiative and the EMA Cross-Committee Task Force on Registries took up the stakeholders' request and gained even more recommendations and information specific for registry-based studies. All this information flew into the new "*Guideline on registry-based studies*" published in 2021, which provide requirements and recommendations on key methodological aspects specific to the conduct of registry-based studies by MAA/MAH. Although, the guideline is not specific to ATMPs, it is particularly relevant for ATMP MAA/MAH, because on the one hand often not all safety data are available at the time of marketing authorisation and on the other hand the number of patients treated is usually quite small, making further tracking and generation of long-term effects difficult.

The guideline firstly provides general information on important methodological differences between a registry-based study and a patient registry. Whereas the registry-based study is defined as an "*Investigation of a research question using the data collection infrastructure or patient population of one or more patient registries*" the patient registry is an "*Organised system that collects uniform data (clinical and other) to identify specified outcomes for a population defined by a particular disease, condition or exposure*" (Art. 3.1 (32)). Furthermore, examples are given for which purpose registry-based studies can be accepted as a source of evidence for regulatory purposes. One example is to provide evidence in the post-authorisation phase, what is especially relevant for ATMPs developers (Art. 3.2 (32)). Concerning the planning of a registry-based study, the guideline specifies a lot of points to consider and to include in the study protocol. After the identification of the scientific question(s) to be addressed by the study and a critically consideration if a registry-based study is the appropriate choice (an early discussion with NCAs and EMA is additionally recommended), the MAAs/MAHs firstly have to identify one or several suitable registry(-ies) and to obtain an agreement to collaborate from each of them. Furthermore, a feasibility analysis should be considered by the MAA/MAH prior to writing the study protocol in collaboration with registry

holders. Information to be included in the feasibility analysis and submission and publication details for the final feasibility report are specified as well. The guideline also encourages MAHs to design a joint registry-based study or to join an already existing study, if applicable (Art. 3.3 (32)).

In the next step, the guideline further specifies the structure and content of the study protocol and mentions topics specific to registry-based studies, like a justification of the choice of the registries used for the study (Art. 3.4 (32)). The guideline also provides guidance on how to choose the study population, which can represent the totality of the registry population or only a subset with pre-defined characteristics. In case of study-specific primary data collection within an existing registry, a complete data collection on all eligible patients enrolled in the registry has to be applied. Furthermore, an informed consent has to be obtained from patients to participate in the study in addition to the consent already given for participating in the registry, as applicable. Requirements for personal data protection as well as for data collection are also provided (Art. 3.5 (32)). Thereby, two types of data are discussed: data already collected in the registry (secondary use of data) and additional study-specific primary data (Art. 3.6 (32)). Furthermore, the guideline specifies the data quality management of the registry-based study, like data verification and corrective actions, which should be discussed and accepted by the MAA/MAH and the registry holder (Art. 3.7 (32)). An evaluation of the representativeness of the study population in relation to the source population is also mandatory, if it is relevant for the external validity of the registry-based study. Furthermore, common analytical issues which should be addressed in the absence of randomised treatment allocation in registry-based non-interventional studies are discussed (Art. 3.8 (32)). Additionally, requirements for the study registration and data reporting are specified (Art. 3.9 (32)). As a further support for MAAs/MAHs, the legal basis and regulatory requirements applicable for different activities related to registry-based studies are summarised. Thereby, the different activities of the MAA/MAH and the different types of registry-based studies are distinguished in order to give a good overview of the various requirements (Art. 4 (32)). Interestingly, the guideline mentions that in some situations registry data can be shared outside the context of formal registry-based studies. For example, safety information on medicinal products, like summary tables of adverse events for specific medicinal products or anonymised line listings of patients presenting adverse events of specific interest, can be shared under certain requirements (Annex I (32)). The guideline provides a solid orientation for all ATMP MAAs/MAHs who

are considering collecting long-term post-marketing data with registry-based studies. It offers good support in assessing whether this type of data collection is suitable for the respective question and thus offers the possibility of obtaining specific patient data more easily and reliably. Even if the guideline is not specifically aimed at ATMPs, it is probably also particularly relevant for this type of medicinal products, as the follow-up of all patients is mandatory here and is particularly difficult due to the often long observation periods required.

4 Discussion and Recommendations

This chapter summarises the results presented in chapter 3 and critically discusses to what extent the stakeholders' requests have been considered and whether the corresponding points of the action plan have been implemented six years after the EC's and EMA's Action Plan on ATMPs has been published. The leading questions are: Are all identified stakeholders' issues addressed? Are regulatory gaps still existing six years after the publication of the Action Plan? Additionally, recommendations are provided, if points of the action plan are not implemented properly.

4.1 Facilitating research and development

Due to the fact, that general scientific guidelines for medicinal products for human use are often not suitable for the specific characteristics of ATMPs, the Regulation (EC) 1394/2007 had already demanded in 2008 new guidelines specific to ATMPs. Additionally, the facilitation of research and development of ATMPs was one of the main issues which were discussed in the EMA's stakeholders workshop in 2016 (see chapter 1.4). The difficulty still is, that on the one hand, developers often need distinct specifications to carry out their development in compliance with the requirements, especially due to a fact, that ATMPs are often developed by SMEs or universities, which lack experience and regulatory expertise. On the other hand, the development of ATMPs requires greater flexibility which is reflected in more product- and risk-specific requirements, due to a high diversity and specific characteristics of ATMP in comparison to common medicinal products. ATMPs are more complex and heterologous products with some degree of variability in the finished product due to the use of biological materials and/or complex manipulation steps (e.g. cultivation of cells, manipulations that alter the function of the cells, etc.) and with risks which may differ according to the product type, nature/charac-

teristics of the starting materials and level of complexity of the manufacturing process. In addition, the manufacture and testing of autologous ATMPs poses specific challenges like the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material (Art. 2.1 (22)).

The first and biggest milestone of the Action Plan is the guidance document "*Eudralex Volume 4 - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products*" published in 2017 and addressing several stakeholders' issues from the topic "*Facilitating research and development*". The first benefit of the guidelines is a detailed description of the risk-based approach (RBA) for the manufacturing process and the introduction of several exceptions, especially in the early development phase. The guidelines consider that ATMPs are complex products with risks differing according to the product type (TEP, GTMP or sCTMP), characteristics of the starting materials and level of complexity of the manufacturing process. It is also acknowledged that the manufacturing and testing of autologous ATMPs poses specific challenges. In order to illustrate the application of the RBA to ATMPs, examples are given in connection with the raw materials, with the test strategy, with ATMPs that have not been substantially modified and with investigational ATMPs. Thereby, important proposals of the stakeholders were realized: More guidance concerning the RBA, especially for the Qualified Persons (QPs), and more flexibility during the early development phase. But of cause, the given examples cannot cover all ATMPs types and therefore only a first orientation for the implementation of the RBA is provided. This means that developers have to transfer the principles to their own product, what leaves room for interpretation and makes the consultation with the EMA still necessary. One way to offer more support to the developers at this point would be to publish a Q&A document based on the outcomes of all scientific advices and certification procedures by the EMA on a regular basis for all member states in order to give developers the opportunity to orientate themselves on questions already discussed. Thereby, a large knowledge base could be created over time helping the developers to find their own approach.

Another stakeholders' request, the harmonisation of requirements for cells and tissues used as starting materials, for excipients and raw materials is only partly met by the guidelines. On the one hand, requirements for the verification of cells and tissues used as starting materials, the establishment of specifications for the starting materials and the compliance controls are

provided. But on the other hand, many of these requirements are not very concretely formulated and are based on the RBA, which naturally grants a high flexibility. Thereby, no real standardisation and harmonisation is achieved. Furthermore, the guidelines reference already existing guidelines on human tissues and cells in large parts without providing real new requirements in terms of starting materials. It is therefore doubtful, if the guidelines can solve the problem of missing harmonisation of the requirements for cells and tissues as starting materials. A first step towards harmonisation could be the publication of a "*Compilation of Union Procedures on Inspections and exchange of Information*" (last update 06/2023) by the EMA in order to facilitate the co-operation between the GMP and GDP inspectorates of the Member States and to provide a basis for national procedures that form part of the national GMP inspectorates' quality systems.

Furthermore, the guidelines provide more specific, systematic and structured instructions concerning personnel, premises, equipment and documentation for the manufacturing process. Thereby, more precise orientation is provided to the ATMP developers and several stakeholders' proposal are addressed, like licensing requirements consider the unique particularities of ATMP manufacture (ATMP manufacturing at various sites and sites close to the bedside at hospitals) and using a site master file at every site for excipients and raw materials in order to facilitate the proof of GMP compliance. The manufacturing at various sites is also considered in connection with the batch release by providing specific additional requirements, including a Qualified Person for every ATMP manufacturing site involved and the identification of a "*central site*", which has to review and monitor the further manufacturing sites. Finally, the guidelines introduce the possibility to reconstitute ATMPs after batch release at the administration site (bedside) outside a GMP environment and thereby provide the needed flexibility requested by stakeholders. Furthermore, the more specific requirements could also contribute to harmonisation in the Member States.

Another stakeholders' request which is addressed by the guidelines is more flexibility during the early developmental phase, especially for low-risk (non-substantially manipulated) cell-based products. By accepting equivalent standards for the manufacturing process of ATMPs, which does not involve substantial manipulation, the guidelines help to reduce administrative burden. Furthermore, the guidelines grant a whole series of exceptions giving ATMP manufacturers flexibility in many areas and making the requirements more suitable for ATMPs. One

of the new exemptions is, that manufacture can start from already available cells or tissues, which have been processed/manufactured outside of the GMP environment during initial steps, if it is impossible to replace them. Additionally, in exceptional cases and due to the often short shelf life of ATMPs, the batch release can be performed already before the results of all quality control tests are available. The guidelines also bring flexibility concerning the handling of unplanned deviations during the manufacturing process and the administration of out of specification products. In addition, alternative options and flexibility in sterilisation und its validation is provided, a typically issue specific to ATMPs. Thereby, support and orientation for ATMP manufacturers is available, if no conventional product sterilisation is possible. Exemptions for investigational ATMPs are considered in various contexts as well in order to facilitate and accelerate ATMP development, especially at early stage. As an additional new ATMP specific facilitation, requirements for rejected materials are mentioned, including the option of reprocessing of rejected authorized and investigational products under certain circumstances. Thereby, ATMP specific challenges such as high production costs and the scarcity of starting materials are considered giving the manufacturer the possibility to use materials for production more carefully and better safeguard ongoing supply chain. More detailed requirements for handling of quality defects and product recalls help to ensure faster processing of quality defects and increasing patient safety. By considering the automated production of ATMPs, the guidelines also address the stakeholders' request for guidance on technologies to commercial manufacture.

The guidelines also take up the important stakeholders' issue of different requirements for GMOs among the Member States and the integration of GMO assessment in multicenter clinical trials. By introducing environmental control measures for ATMPs depending on four environmental risk levels, a first orientation is provided to the ATMP manufacturers. But unfortunately, the four risk levels are not further specified and no specific control measures are allocated to them. This results in further room for interpretation and therefore raises doubts, that these requirements are sufficient for harmonisation of GMO requirements. A precise definition and criteria for the four risk levels with examples and a clear allocation of mandatory control measurements to them would have been more helpful.

Unfortunately, the stakeholders' issue of upgrading immature developmental production is not specifically addressed by the guidelines. As it is already very difficult for ATMP developers

to fulfil GMP requirements on a smaller scale, upscaling is a big challenge, because the costs and the required premises for the specific manufacturing of ATMPs are often not affordable for SME and universities. In order to keep costs low and to ensure the quality of ATMPs on a larger manufacturing scale, the establishment of specialised and funded service centers, which handle the GMP-compliant manufacturing of investigational ATMPs, could be a possible solution and support for manufacturers and accelerate the ATMP development.

Further important new guidelines published by the EMA in 2019 are the "*GCP guidelines specific for ATMPs*". Already request by the Regulation (EC) No 1394/2007, the guidelines were requested again by the ATMP stakeholders, because the design of clinical trials with ATMPs was identified as one of the biggest challenges in ATMP development. Overall, the guidelines address many stakeholders' concerns from the field of clinical development. The first issue, which is considered is the difficult benefit-risk assessment of ATMPs. But unfortunately, the guidelines do not meet the concern of the stakeholders. Instead of focusing on the expected but realistic benefits of the ATMP and the assessment of them, ATMP specific risks are listed and further discussed. It would have been more helpful, if ATMP specific benefits, like a possible treatment for an incurable disease without alternatives, would have been listed and discussed as well.

On the other hand, the stakeholders' concern "*low patient number due to rare disease indication*" is considered by the guidelines. In order to give further orientation to ATMP developers, a list of particular ATMP specific considerations for the study population is provided. This could help to work out more precise inclusion and exclusion criteria for the study population and to generate more reliable data. But unfortunately, the most important challenge in this context, the difficult subject recruitment due to rare disease indications, is not particularly addressed. A more helpful support would have been, for example, the introduction of the use of specific patient registers for (rare) diseases. Additionally, a broader education of the population and regular information events for specific patient groups and relatives by hospitals, specified facilities and the competent authorities could also help to reduce concerns and fears about study participation on the one hand and to strengthens trust and to make advantages clear on the other hand.

The urgently needed flexibility concerning the study design is provided by the guidelines. The stakeholders' issue "*lack of suitable animal models*" is also addressed by listing ATMP specific

points to consider and providing alternative ways to specify dose ranges for early phase clinical trials, if suitable animal models are not capable. For example, a rationale for a dose definition based on published literature data is introduced in such cases, if a thorough analysis of the comparability between products is provided. But unfortunately, concrete guidance on decision making for choosing a specific study design or a concrete statistical model for randomisation is pending. Providing a concrete decision tree for choosing a study design and randomisation methods based on the product characteristic and suitable animal models would have been more helpful.

The stakeholders' issue "*lack of study personnel with ATMP-specific knowledge*" is picked up more adequately. Instructions and training for study personnel on complex handling processes, reconstitution and application of investigational ATMPs are introduced as new requirements. This information serves as a good orientation for ATMP developers, but unfortunately precise education concepts concerning clinical trials with ATMP on a more general level and with documented evidence on a regular basis is pending. It is therefore questionable how these requirements should be implemented and monitored sustainably. A specific curriculum with defined content as a basis for regular courses for study staff would be the next step for a sustainable implementation.

A new exemption, which is introduced by the GCP guidelines is the possibility of administration of out of specification investigational ATMPs to avoid an immediate significant hazard to the subject. This is an important adaption, because ATMPs can be used in rare indications where no alternative therapy is available. It also considers that starting material is often scarce for ATMP production and therefore resources must be used with particular care.

In order to adapt also the requirements for post-market development to the stakeholders' issues, the EMA has started to update the "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products*" in 2018. The currently existing draft version of the revised guideline provides more detailed guidance on the safety and efficacy aspects, which have to be considered in the risk management plan, including a list of risks with updated examples considering new technologies. Additionally, risk minimization measures are specified in more detail, like the educational program for treating physicians, pharmacists, patients and others as well as considerations on (long term) efficacy and safety follow-up of ATMPs. This could help the developers to transfer the requirements to your own product and

accelerate the development process. Overall, the revision does not introduce real new requirements for the follow-up of ATMPs, which means that no new regulatory hurdles are created.

In 2020 the EMA also revised the "*Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells*" in order to include the recent developments and the latest technologies. While the quality section picks up several points already introduced and discussed in the new GMP guidelines specific for ATMPs, no really new aspects are introduced and discussed. The only new exemption seems to be the two-step release program, which may be carried out when some release data are available only after administration of the product. This exemption represents a necessary adaption and will facilitate the development and marketing authorisation of ATMPs. The non-clinical and clinical sections of the guideline have also been adapted to the latest state of technology and supplemented with some examples of current developments. These can serve as orientation and support the developers in preparation of preclinical and clinical development plans.

4.2 Optimising the regulatory processes for ATMPs

Due to the stakeholders' proposal to streamline the EMA internal regulatory process for ATMPs, an update of the guidance document "*Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007*" has been realized. The aim was to clarify the evaluation procedure and to help developers of ATMPs to navigate the regulatory process in the EU and implemented by a more detailed description of the evaluation process. Beside introducing the role of the PRAC in the assessment process, the roles and responsibilities of all involved committees are specified more clearly. Additionally, procedural aspects, like processes for adopting questions during the evaluation and the process for oral explanation, were streamlined a bit far. As a facilitation for applicants, extended clock stops were introduced as well. But overall, there are no profound changes in the process itself, for examples, in the timelines or the communication procedures between the EMA and the associated committees. Therefore, it is still questionable whether the applicants can follow the initiated process, are informed about the status and have a contact person available at all times. Also, because the document seems to be written from the point of view of the authorities, it would also make sense to draw up a guidance

document that addresses the applicants directly and presents and advises the evaluation process from their perspective.

In addition, the EMA has developed the new multidisciplinary "*Guideline on quality, non-clinical and clinical requirements for investigational ATMPs in clinical trials*", which is available as a draft since 2019. The guideline provides guidance on the structure and data requirements for a clinical trial application, including more flexible quality data requirements, especially in the early development phase. The possibility to use non-pharmaceutical grade excipients in exceptional cases and to rely on intermediate product release criteria in the case of limited amount of final product are new and more flexible requirements. But several essential points of the guideline, like the evolving data requirements and the gradual approach for process improvement and validation were already introduced by the GMP guidelines specific to ATMP, which are also relevant for investigational ATMPs, and therefore bring no additional added value for the developers.

In the field of non-clinical data documentation, the guideline makes a bigger difference in comparison to previous ones. The stakeholders' request for orientation concerning the study design is addressed in more detail by providing ATMP specific recommendations, including the route of administration and the application procedure, dose levels tested and animal models used. Additionally, the stakeholders' request for considering modern technologies was considered by the introduction of cell- and tissue-based models, including 2D and 3D tissue-models, organoids and microfluidics as alternatives to animals. It is considered, that it would not always be possible to conduct studies in full conformity with GLP and therefore a minimum set of non-clinical data requirements before first-in-human studies as well as non-clinical data that can be provided at later stages of development are provided.

In connection with the clinical data the guideline addresses the two stakeholders' issues "*benefit-risk-assessment*" and "*study design specific for ATMPs*". In contrast to the GCP guidelines specific to ATMPs, which focused on the risks during the benefit-risk-assessment for clinical trials, the new guideline also mentions the anticipated effect and the available treatment options as well as the medical need. Thereby, the benefits are also considered, even if the focus is still on the risks. In general, it can be said that the guideline takes up many points that are already included in the GCP guidelines specific to ATMPs, but explains them in more detail.

This could be further support for the ATMP developers with planning clinical trials and submitting the corresponding application.

In 2021 the EMA published the "*Guideline on registry-based studies*". Although this guideline is not specific for ATMPs, it addresses the ATMP stakeholders' proposal to use disease registries in order to monitor safety, to collect structured data and meet pharmacovigilance and post-authorisation requirements. After the possibility of using patient registers for post marketing studies was first mentioned in the guideline draft "*Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products – Revision 1*", it is now defined in more detail and provides a basic orientation to marketing authorisation applicants/holders. It is specified when registry-based studies can be considered and what needs to be considered in this case. This represents a real facilitation, especially for ATMP developers, who often have to deal with specific challenges like rare disease indications and long observation periods.

5 Conclusion

Six years after the publication of the EC's and EMA's Action Plan it can be stated that most of the identified stakeholders' issues are addressed by several new guidance documents specific to ATMPs, but nevertheless some of the main problems which are mentioned in the following are still not sufficiently solved.

Of all new guidance documents based on the Action Plan, the "*GMP guidelines specific to ATMPs*" are expected to have the greatest positive impact on the development of ATMPs in the EU, because this guidance document is the most comprehensive one and addresses the most stakeholders' issues. But although the guidelines consider many suggestions and introduces highly needed adaptations and exceptions in many places, it is doubtful whether it can solve some fundamental problems, such as insufficient knowledge of developers about the regulatory requirements in connection with GMP-compliant manufacturing cannot be built up by even the best guidelines alone. To achieve this, additional comprehensive training concepts have to be developed in order to familiarise researchers and developers and other stakeholders with the GMP requirements and the purpose behind them at an early stage. This could be a first step to reduce the gap between innovative research and product development and to facilitate the translation from the preclinical to the clinical development phase. Additionally,

to set up a dedicated EMA office for academia with expertise in ATMPs and to open up the certification procedure to non-SME would be necessary actions, which are still pending. Another still pending approach would be to outsource the GMP-compliant manufacturing to funded ATMP specific manufacturing sites, which are available for SME/universities and harmonised across the Member States. In addition, a still missing harmonisation of specific requirements across the Member States (GMO, cells and tissues used as starting materials, raw materials and excipients) still seems to be one of the biggest hurdles in the development of ATMPs. As these main obstacles to the development of new innovative ATMPs have not yet been removed, it is doubtful that the measures implemented so far under the actions plan will have a major impact on the number of further marketing authorisations for ATMPs in the EU.

The latest and biggest initiative of the European Commission is a proposal for a new "*Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency*" published in April 2023, which is relevant for centrally authorised medicinal products, including ATMPs and complementing the Regulation (EC) 1394/2007. Two main aims of the new Regulation are to "*offer an attractive innovation-and competitiveness friendly environment for research, development, and production of medicines in Europe*" and to "*make medicines more environmentally sustainable*" with focus on medicinal products for rare diseases and children (33). Thereby, topics are addressed which are also especially relevant for ATMPs. But whether this will make a real difference for the ATMP development in the EU in the coming years remains to be seen.

6 Summary

Advanced Therapy Medicinal Products (ATMPs), including Tissue Engineered Products (TEPs), Gene Therapy Medicinal Products (GTMPs) and somatic Cell Therapy Medicinal Products (sCTMP), are developed since approximately forty years and offer great clinical perspectives for unmet medical needs and rare diseases. But nevertheless, currently only 18 ATMPs have got a marketing authorisation valid in the European Union (EU), including two TEPs (17). In order to identify the key issues in ATMP development, the EMA hosted a workshop for stakeholders with diverse backgrounds in May 2016. Based on the issues identified, the European Commission and the EMA published an Action Plan on ATMPs in October 2017 in order to initiate certain follow-up actions to improve and to facilitate the development and the marketing authorisation of innovative ATMP in the EU (20). The proposed actions target challenges identified at all stages of development and include several services and activities as well as guidance documents specific on ATMPs (20).

This thesis provides a comparison of the European legislative landscape concerning ATMPs, especially TEPs, before and six years after the European Commission's and EMA's Action Plan on ATMPs has been published. In addition, it is assessed which points of the action plan have already been implemented. Seven new or revised guidance documents are further reviewed to determine whether the previously identified stakeholders' issues have been sufficiently addressed. Overall, it can be stated that the assessed guidelines reflect many suggestions and introduces highly needed adaptations and exceptions in many places. Of these guidance documents, the "*GMP guidelines specific to ATMPs*" are expected to have the greatest positive impact on the development of ATMPs in the EU, because it is the most comprehensive one and addresses the most stakeholders' issues. But in summary it can be said that some of the biggest hurdles in the development of ATMPs, like the missing harmonisation of specific requirements across the Member States (GMO, cells and tissues used as starting materials, raw materials and excipients) are still unaddressed. Therefore, it is questionable whether the measures implemented so far under the actions plan will have a major impact on the number of further marketing authorisations for ATMPs in the EU.

7 References

1. THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Official Journal of the European Communities L 311/67-128, 28.11.2001

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:311:0067:0128:en:PDF (accessed 22.01.2024)

2. THE COUNCIL OF THE EUROPEAN COMMUNITIES. COUNCIL REGULATION (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products. Official Journal of the European Communities No L 214/1-21, 24.08.1993

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31993R2309 (accessed 22.01.2024)

3. https://www.ema.europa.eu/de/documents/product-information/holoclar-epar-product-information_de.pdf. (accessed 07.04.2024)

4. https://www.ema.europa.eu/de/documents/overview/spherox-epar-summary-public_de.pdf. (accessed 07.04.2024)

5. https://www.ema.europa.eu/de/documents/product-information/abecma-epar-product-information_de.pdf. (accessed 07.04.2024)

6. https://www.novartis.com/at-de/sites/novartis_at/files/GI_Zolgensma.pdf. [Online]

7. https://www.ema.europa.eu/en/documents/product-information/alofisel-epar-product-information_en.pdf. (accessed 07.04.2024)

8. https://www.ema.europa.eu/de/documents/product-information/ebvallo-epar-product-information_de.pdf. (accessed 07.04.2024)

9. THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. Official Journal of the European Union L324/121-137, 10.12.2007

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF (accessed 22.01.2024)

10. THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. DIRECTIVE 2004/23/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. Official Journal of the European Union L 102/48-58, 07.04.2004

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:102:0048:0058:en:PDF (accessed 22.01.2024)

11. THE COMMISSION OF THE EUROPEAN COMMUNITIES. DIRECTIVE 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells. Official Journal of the European Union L 38/40, 09.02.2006

https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ%3AL%3A2006%3A038%3A0040%3A0052%3AEN%3APDF (accessed 22.01.2024)

12. THE COMMISSION OF THE EUROPEAN COMMUNITIES. COMMISSION DIRECTIVE 2006/86/EC of 24 October 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirement. Official Journal of the European Union L 294/32-50, 25.10.2006

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006L0086 (accessed 22.01.2024)

13. THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION. Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. Official Journal of the European Union L 242/3-12, 15.09.2009

https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:242:0003:0012:EN:PDF (accessed 22.01.2024)

14. COMMITTEE FOR MEDICINAL PRODUCT FOR HUMAN USE (CHMP). GUIDELINE ON HUMAN CELL-BASED MEDICINAL PRODUCTS. Doc. Ref. EMEA/CHMP/410869/2006, 21.05.2008

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-human-cell-based-medicinal-products_en.pdf (accessed 22.01.2024)

15. European Medicines Agency, Committee for Advanced Therapies (CAT). Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products. EMA/CAT/CPWP/686637/2011, 11.02.2013

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-risk-based-approach-according-annex-i-part-iv-directive-200183ec-applied-advanced-therapy-medicinal-products_en.pdf (accessed 22.01.2024)

16. European Medicines Agency COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP). GUIDELINE ON SAFETY AND EFFICACY FOLLOW-UP - RISK MANAGEMENT OF ADVANCED THERAPY MEDICINAL PRODUCTS. Doc. Ref. EMEA/149995/2008, 20.11.2008

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-safety-and-efficacy-follow-risk-management-advanced-therapy-medicinal-products_en.pdf (accessed 22.01.2024)

17. vfa bio Die forschenden Pharma-Unternehmen. Übersicht über zentralisiert in der EU zugelassene ATMP. s.l., 19.12.2023

https://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/atmp (accessed 22.01.2024)

18. Mohammed Abou-El-Enein, Ahmed Elsanhoury, Petra Reinke. Overcoming Challanges Facing Advanced Therapies in the EU Market. *Cell Stem Cell 19.,* 01.09.2016

https://www.cell.com/cellstemcell/fulltext/S19345909(16)302594?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS1934590916302594%3Fshowall%3Dtrue (accessed 22.01.2024)

19. European Medicines Agency. Advanced therapy medicines: exploring solutions to foster development and expand patient access in Europe Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Friday 27 May 2016. *Outcome of a multi-stakeholder meeting with experts and regulators held at EMA on Friday 27 May 2016.* EMA/345874/2016, 03.06.2016

https://www.ema.europa.eu/en/documents/report/outcomes-workshopmultistakeholderadvanced-therapy-medicinal-products-atmps-expert-meeting-exploring-solutions-foster-atmps-development-and-patient-access-europe_en.pdf (accessed 22.01.2024)

20. European Commission DG Health and Food Safety and European Medicines Agency. European Commission DG Health and Food Safety and European Medicines Agency Action Plan on ATMPs. s.l., 20.10.2017

https://www.ema.europa.eu/en/documents/other/european-commission-dg-health-and-food-safety-and-european-medicines-agency-action-plan-advanced-therapy-medicinal-products-atmps_en.pdf (accessed 22.01.2024)

21. European Medicines Agency. Issues identified by stakeholders: follow-up from EMA's ATMP workshop. EMA/48099/2017, 02.02.2017

https://www.ema.europa.eu/en/documents/other/issuesidentifiedstakeholdersworkshopmultistakeholder-advanced-therapy-medicinal-products-atmps-expert-meeting-exploring-solutions-foster-atmps-development-and-patient-access-europe_en.pdf (accessed22.1.24)

22. European Commission. EudraLex The Rules Governing Medicinal Products in the European Union Volume 4 Good Manufacturing Practice - Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products. s.l, 22.11.2017

https://health.ec.europa.eu/system/files/2017-11/2017_11_22_guidelines_gmp_for_atmps_0.pdf (accessed 22.01.2024)

23. European Medicines Agency, Committee for Human Medicinal Products. ICH guideline Q10 on pharmaceutical quality system. EMA/CHMP/ICH/214732/2007, September 2015

https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-guideline-q10-pharmaceutical-quality-system-step-5_en.pdf (accessed 22.01.2024)

24. European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP). Guideline on safety and efficacy follow-up and risk management of Advanced Therapy Medicinal Products Draft. EMEA/149995/2008 rev.1, 25.01.2018

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-safety-and-efficacy-follow-and-risk-management-advanced-therapy-medicinal-products-revision-1_en.pdf (accessed 22.01.2024)

25. European Medicines Agency, Human Medicines Research and Development Support Division. Issues identified by stakeholders: follow-up from EMA's ATMP workshop. EMA/48099/2017, 02.02.2017

https://www.ema.europa.eu/en/documents/other/issues-identified-stakeholders-workshop-multi-stakeholder-advanced-therapy-medicinal-products-atmps-expert-meeting-exploring-solutions-foster-atmps-development-and-patient-access-europe_en.pdf (accessed22.1.24

26. Renske M.T. ten Ham, Jarno Hoekman, Anke M. Hövels, Andre W. Broekmans, Hubert G.M. Leufkens. Challenges in Advanced Therapy Medicinal Product Development: A Survey among Companies in Europe. *Molecular Therapy Methods & Clinical Development Volume 11 page 121-130,* 12.2018

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6234262/pdf/main.pdf (accessed 22.01.2024)

27. Cécile F. Rousseau, Romaldas Maciulaitis, Dariusz Sladowski and Gopalan Narayanan. Cell and Gene Therapies: European View on Challenges in Translation and How to Address Them. Frontiers in Medicine Volume 5 Article 158, 28.05.2018

https://doi.org/10.3389/fmed.2018.00158 (accessed 22.01.2024)

28. European Commission. Guidelines on Good Clinical Practice specific to Advanced Therapy Medicinal Products. C(2019) 7140 final, 10.10.2019

https://health.ec.europa.eu/system/files/2019-10/atmp_guidelines_en_0.pdf (accessed 22.01.2024)

29. European Medicines Agency, Committee for Advanced Therapies (CAT). Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells. EMA/CAT/GTWP/671639/2008 Rev. 1 - corr, 12.11.2020: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-quality-non-clinical-and-clinical-aspects-medicinal-products-containing-genetically-modified-cells-revision-1_en.pdf (accessed 22.01.2024)

30. European Medicines Agency. Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 of Regulation (EC) No 1394/2007. EMA/630043/2008, 25.01.2018

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/procedural-advice-evaluation-advanced-therapy-medicinal-product-accordance-article-8-regulation-ec-no-13942007_en.pdf (accessed 22.01.2024)

31. European Medicines Agency, Committee for Advanced Therapies (CAT). Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials Draft. EMA/CAT/852602/2018, 31.01.2019

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-quality-non-clinical-and-clinical-requirements-investigational-advanced-therapy-medicinal-products-clinical-trials_en.pdf (accessed 22.01.2024)

32. European Medicines Agency, Committee for Human Medicinal Products (CHMP). Guideline on registry-based studies. EMA/426390/2021, 22.10.2021

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en.pdf-0 (accessed 22.01.2024)

33. European Commission. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL laying down Union procedures for the authorisation and supervision of medicinalproducts for human use and establishing rules governing the European Medicines Agency. COM(2023) 193 final 2023/0131 (COD), 26.4.2023

https://eur-lex.europa.eu/resource.html?uri=cellar:e3f40e76-e437-11ed-a05c-01aa75ed71a1.0001.02/DOC_1&format=PDF (accessed 22.01.2024)

8 Eidesstattliche Erklärung

Erklärung

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Wegberg, den

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Unterschrift Dr. Sabine Küppers