How to develop a fictitious combined ATMP regarding non-clinical and early clinical phase: A possible SME Scenario

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1 Introduction

The steady progress of science and research over the last decades has promoted the development of advanced therapy medicinal products (ATMP), a special group of medicinal products, which – according to current legislation – as a common feature are exclusively based upon gene therapy, somatic cell therapy or tissue engineering and which are usually designed to treat life-threatening or severely debilitating diseases.
Gene therapy medicinal products (GTMP), somatic cell therapy medicinal products (sCTMP) and tissue engineering products (TEP) are respectively defined in Annex I, Part IV, 1 and 2 of Dir. 2001/83/EC and in Reg. (EC) 1394/2007 Art. 2(1)b.
The latter one is the result of an amendment of Dir. 2001/83/EC and EC Reg. No. 726/2004 designed under the Commission's surveillance, in order to address and define specific aspects of the content of the Marketing Authorisation Application (MAA) dossier of ATMP. Apart from the Regulation the ATMP regulatory framework consists of a number of continuously revised product-specific, legally non-binding guidelines, procedural advice documents and recommendations. For better overview and understanding this framework will be outlined in the following sections.
The assessment of MAAs from a high number of enterprises dedicated to the development of ATMP usually requires extensive expertise, which is highly treatment-specific as well as involves deep knowledge of disciplines beyond conventional biotechnology such as bioengineering, medical devices or surgical procedures. For this reason the Commission obliged the European Medicines Agency (EMA) to set up the Committee for Advanced Therapies (CAT), an expert Committee whose main responsibility is to prepare draft opinions on ATMP applications submitted to the EMA and who cooperates specifically with other Committees and stakeholders (e. g. the Committee for human medicinal products (CHMP) for final opinions, notified bodies (NB) for expertise potentially needed for integral medical devices, health technology assessment (HTA) bodies etc.). The CAT experts coming from multi-disciplinary fields have facilitated the approval of five different products (out of 13 MAAs) since 2009, namely ChondroCelect (TEP), Glybera (GTMP), MACI (combined TEP), Provenge (sCTMP) and – approved in February 2015 by the CHMP – Holoclar (TEP containing stem cells) (Forum Institut 03/2015).

Other than in case of chemical medicinal products the development of a universally valid non-clinical and clinical safety and efficacy program is not feasible for ATMP. Research and development of ATMP depend on the specific nature of each product and need to be designed on a flexible case-by-case basis in order to meet the high diversity of products and the risks and chances related thereto.

In this thesis a combined ATMP consisting of genetically modified viable allogeneic human cells exerting the principal mode of action and an implantable non-active medical device, which delivers the GTMP, is to be described with special emphasis on the appropriate way of its scientific development during non-clinical and early clinical phase as well as on the requirements and possibilities that are defined by the current legal landscape within the European Union.

2 Overview of the legal and regulatory landscape governing ATMP

2.1 Legislation

The following sections aim at providing an overview of the complex legal landscape regarding both legally binding and non-binding provisions and recommendations that determine the way of a combined ATMP with an integral medical device part from non-clinical to early clinical phase.
Since in many cases innovative developments in the biotechnological field, especially in the group of advanced therapies, have their roots in the laboratories of micro, small and medium-sized enterprises (SME) the activities of the EMA's SME office and their consequential role in drug development will also be mentioned.

2.1.1 Assignment of the combined ATMP in question according to current pharmaceutical law

In December 2008 the ATMP regulation (EC) No. 1394/2007 came into effect as an amendment to Dir. 2001/83/EC and EC Reg. No. 726/2004 to be applied for ATMP that are "to be placed on the community market and (that are) either prepared industrially or manufactured by a method involving an industrial process". GTMP, sCTMP and TEP as mentioned in section 1 of this thesis were defined as ATMP and specifically determined pathways for these therapeutical groups were laid down as a rule to protect patients from scientifically unsound treatments and to create a common framework for the assessment of advanced therapies in the EU. Along those pathways a centralised authorisation procedure with decisive involvement of the CAT was stated and special incentives for small and medium-sized enterprises were fixed to meet the requirements of ATMP researchers, who often lack appropriate funding and the capacity for corresponding regulatory expertise.
Regarding combined ATMP a specific definition has been incorporated into the regulation represented by Art. 2(1)(d), (2) and (3), which define 'Combined advanced therapy medicinal products' as an ATMP fulfilling the following conditions:

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

(2) Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product.
(3) An advanced therapy medicinal product containing both autologous (emanating from the patient himself) and allogeneic (coming from another human being) cells or tissues shall be considered to be for allogeneic use."

When taking account of this definition regarding a combined ATMP containing a gene therapy medicinal product it has to be read in conjunction with the definitions of GTMP laid down in Annex I of Directive 2001/83/EC and with the aforementioned Medical Device Directive 93/42/EEC. The Directive 90/385/EEC does not apply in this case because the product of concern does not contain an active implantable medical device intended to administer or exchange energy. However, Article 1(2)(a) of Directive 93/42/EEC defines the medical device part of this product as it represents "any instrument, (…), whether used alone or in combination, (…) intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, monitoring, treatment, alleviation or of compensation for an injury or handicap,
- investigation, replacement or modification of the anatomy or of a physiological process, (…)

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

In the product concerned such means are performed by the GTMP part, which is intended to be delivered by the medical device. This makes Article 1(3) of Directive 93/42/EEC applicable to the product where it is stated that in such a case also the medical device part "shall be governed by Directive 2001/83/EC" provided that "the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable (…)". If this is not the case or if the GTMP merely exerts an action ancillary to the action of the device, the device would be governed by Directive 93/42/EC by law. The conclusion to be drawn from this evaluation of legal provisions is also in line with Articles 6(1) and 9(1) of the ATMP regulation.

Having demarcated the combined ATMP according to current legally binding provisions the product shall be governed by Directive 2001/83/EC as a medicinal product without prejudice to the required fulfilment of the essential requirements set out in Annex I of Directive 93/42/EC applicable for the device part in terms of safety and performance-related features (reference is made to section 2.1.3).
No CE marking, risk classification or mandatory involvement of a notified body is required. The demonstration of acceptable safety and performance of the device needs to be carried out within the frame of non-clinical and clinical studies of the whole medicinal product or, where not covered by such, of specifically designed investigations.

2.1.2 Relevant guidelines, recommendations and procedural advice for combined ATMP incorporating a GTMP

There exists a wide range of authority guidance and recommendations that are permanently revised and updated in order to facilitate development of ATMP for involved enterprises and to ensure the highest possible quality standard of products concerned before investigation and application in humans.

In this section the most important relevant documents having been released by the EMA will be mentioned and described in order to provide an overview fundamental to the scenario sections that are to follow later in this thesis.

2.1.2.1 ATMP and combined ATMP

Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with article 17 of regulation (EC) no 1394/2007 (EMA/CAT/99623/2009 Rev.1) [1]
Potential applicants for ATMP authorisation have the option, in case of doubt, to clarify the classification whether a product based on genes, cells or tissues meets the scientific criteria which define ATMP. It is recommended that this is done as early as possible during development i.e. before request for protocol assistance, certification of quality and non-clinical data, and in any case before submission of MAA. According to the procedural flow the CAT will deliver its 'scientific recommendation on ATMP classification' within 60 calendar days after a valid request, in collaboration with the Innovation Task Force (ITF) that provides operational, scientific, regulatory and legal support to the CAT and after consultation with the European Commission (EC) and, if necessary, with another Scientific Committee or Working party. A decision by these parties is made based on criteria such as origin, type, processing, and function of the cells concerned. Final recommendations will be published by the EMA.
The experience gained in the application of the classification procedure is incorporated in a recently revised reflection paper providing further guidance on the procedure and on the interpretation of key concepts of the definition of GTMP, sCTMP, TEP and combined ATMP (**Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)** [2]).

Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/2008/corr) [3]
This guideline describes a procedure laid down in Article 18 of regulation (EC) no 1394/2007 and specifically invented for SME. Due to its importance within the development process it shall be mentioned at this point of the overview. It intends to define the minimum data content for the so called certification dossier. SME may at any stage of development - as an incentive - submit to the EMA all relevant quality and non-clinical data required according to Annex I of Directive 2001/83/EC, for scientific evaluation and certification. The procedure as a stand-alone evaluation procedure is to offer useful guidance without being directly binding for future MAA or CTA and without reducing the need for any data to be submitted therein. The role of the CAT consists in evaluating compliance with scientific and technical requirements of Annex I of Dir. 2001/83/EC and in certificating the data finalised at the time of the procedure. No assessment of benefit-risk ratio or any prospective advice regarding further development of the product is provided. Such would be reserved for a Scientific Advice. The principles of this guidance are laid down in Commission regulation (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007.

Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing advanced therapy medicinal products (EMA/CAT/418458/2008/corr.) [4]
In accordance with the guideline described before, this procedural advice outlines the timelines and steps to be taken – including possible site visits - by the CAT and by the applicant. It also specifies the situation in case of combined ATMP. Since the incorporated medical device needs to meet the essential requirements mentioned in section 2.1.3 information related thereto should be provided in the certification application. In case a notified body (NB) has already evaluated the device part, the result of this assessment should also be included. If such information is not available at the time of application for certification the check of conformity with the essential requirements will be excluded from the certificate. This especially becomes relevant in terms of interaction and compatibility between cells and the medical device.

To facilitate the closure of this regulatory gap potentially critical for sound development of a combined ATMP a special collaboration of stakeholders can come into effect when considered necessary by the CAT.
According to Article 16 and 17 of the CAT's **Rules of Procedure (EMA/CAT/454446/2008 rev. 1)** [5] "the CAT may decide to consult relevant notified bodies on any question relating to the assessment of the medical device (…) of a combined ATMP." Information on assessments on medical devices done by the notified body should be transmitted to the CAT within one month after request. However, "in those cases where the application for authorisation of a combined ATMP does not include the results of the assessment by a notified body, the CAT, advised by its experts for medical devices, can decide that involvement of a notified body is not necessary." Legal basis thereof can be found in Article 9 of the ATMP regulation. As an additional result the EMA has established the EMA/CAT and Medical Devices' Notified Body (EMA/CAT-NB) Collaboration Group (CG) as a temporary ad hoc specialised advisory group of the CAT. The group consists of independent experts from both fields plus observing representatives from the Commission. The EMA secretariat organises and coordinates the meetings of the CG (laid down in **Mandate, Objectives and Rules of Procedure for the EMA/CAT and Medical Devices' Notified Body (EMA/CATNB) Collaboration Group (CG) (EMA/327938/2010)** [6] and in **Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007 (EMA/354785/2010)** [7]).

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) [8]
As indicated earlier in section 1.1 combined ATMP and ATMP in general require a flexible product-tailored program of development that addresses the respective particularities of their quality (e.g. biologic source, autologous or allogeneic, processing, manufacturing), biological activity (e.g. genetic manipulation or proliferation,

immunogenicity), mode of administration (local or systemic) and exposure duration. These are risk factors that influence substantially the demands for following non-clinical and clinical investigations. Therefore this guideline has been compiled offering and describing a risk-based approach optional for researching enterprises and providing methodological support in performing prerequisite stepwise risk profiling. On the basis of this profiling that needs to be considered as an ongoing process stretching over the whole development process data relating to quality, non-clinical and clinical aspects of the product are to be generated and presented in the later MAA in a meaningful way. Examples of fictitious products are provided in the guideline as a methodological but not technical support (which has to be sought in otherwise released guidance). The approach has to be differentiated from Risk Management Systems and Environmental Risk Assessment for medicinal products, risk analysis typical of medical devices and the risk management applied when addressing principles of GMP, GLP and GCP. Neither does it result in a whole-product categorical risk classification.
Applicants wishing to use the risk-based approach should notify the EMA and the Rapporteurs at an early pre-submission stage and consequentially mention and documentate their approach in the MAA cover letter and dossier.

Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810) [9]
Referring to the mentioned guidance on risk-based approach, risks emerging during clinical application of (combined) ATMP need to be considered very early during the development process in order to be addressed in appropriate non-clinical studies. In consequence products administered to humans (for the first time or repeatedly) have to meet strict requirements outlined in this European Commission guideline. The overarching principles applicable for products containing human cells are traceability in terms of donation, manufacturing and administration as well as follow-up and record-keeping of study subjects during and after the clinical trial for subjects' safety and data collection. Moreover, reference is made to the underlying legislation (e.g. Dir. 2001/20/EC on GCP principles in general; Dir. 2004/23/EC on standards for donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells; ATMP regulation; GMP guidelines), the responsibilities of involved parties (e.g. authorities, Ethics Committee, investigator, sponsor) and the contents of the relevant documentation.

Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008) [10]
Similar principles are addressed in this guideline with emphasis on required aspects of the EU-Risk management plan (EU-RMP) and the Detailed Description of the Pharmacovigilance System (DDPS) regarding safety and efficacy follow-up of ATMP already authorised. The guideline has overarching character (outlining the legal basis, scientific rationale for additional requirements, regulatory tools) and aims at facilitating the ongoing benefit-risk-analysis of ATMP in the post-marketing phase. Thus its content needs to be distinguished clearly from the product-specific risk profiling applied in the risk-based approach described earlier in this section.

2.1.2.2 GTMP

Within the group of GTMP, which are defined in Part IV of Annex I to Directive 2001/83/EC, one product - Glybera for treatment of Lipoprotein lipase deficiency - has gained MA according to the provisions laid down in the ATMP regulation so far.
Research activities are carried out on a high level and scientific knowledge is evolving at a high pace. For this reason and for promotion of the development of sound high quality therapies scientific standards with regard to particular risks attributable to GTMP are needed as far as harmonisation is possible due to the complexity of such therapeutic concepts.
The EMA and the CAT have released a number of guidance documents, of which those relevant for the product issued in this thesis, are summed up in this section.
The CHMP in collaboration with the Gene therapy working party (GTWP) has published a **Questions and Answers** document **on Gene therapy (EMA/CHMP/GTWP/212377/2008)** [11], which provides an overview of authority guidance currently in place.

Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (Draft) (EMA/CAT/80183/2014) [12]
In May 2015 the EMA has released this draft guideline for public consultation. It mainly applies to GTMP containing recombinant nucleic acid sequences or genetically modified micro-organisms or viruses. Thus it does not specifically consider GTMP containing genetically modified allogeneic or autologous somatic cells. Still, the outlined principles apply to modifications of such cells. The guideline addresses specific requirements for pharmaceutical development and manufacturing of a GTMP, non-clinical studies needed along with information on dose selection, route of administration and application schedule for clinical trials and the need for investigation of pharmacological properties, clinical efficacy and safety as required for any other medicinal product.

Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008) [13]
To combined ATMP discussed in this thesis the example for genetically modified cells given in this guideline "genetically modified cells for treatment of monogeneic inherited disease" is applicable (reference is made to section 3). Other genetically modified cells of human or animal origin are dendritic cells and lymphocytes used for cancer immunotherapy, chondrocytes and osteogenic cells for cartilage and bone fracture repair as well as cells for cardiovascular or infectious disease treatment. The guideline covers practically most aspects regarding quality, non-clinical and clinical development, which are also required for novel non-ATMP, specifying points to consider for ATMP and adding topics such as gene transfer and particular clinical follow-up and environmental risk assessment.

Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99) [14]
This guideline offers information on general requirements for product characterisation, applying to different types of gene transfer (bacterial plasmid, viral vector, xenogeneic/allogeneic/autologous cells) with different functions (addition and expression of a gene for therapeutic purposes, inoculation of nucleic acids for vaccination, transfer of nucleic acids to modify the function or expression of an endogenous gene). The design of corresponding products regarding their scientific rationale, quality control during production, provisions to be followed during donation of allogeneic and xenogeneic cells, modalities for *in vitro* cell manipulation and specific aspects during non-clinical and clinical development are described.

Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006) [15]
This guideline was developed on a multidisciplinary basis addressing development, manufacturing, quality-control, non-clinical and clinical aspects of cell-based medicinal products (CBMP). It not only applies to sCTMP but also to the cellular component of products based on allogeneic or autologous cells that may be genetically modified. A comprehensive risk analysis of the whole product to justify development and the evaluation of a number of risk factors (e.g. origin, proliferation/differentiation, immunogenicity, artificial cell manipulation, mode of administration, duration of exposure, knowledge and experience regarding similar products) is recommended. Special consideration is given to the starting materials of cell-based GTMP and reference is made to the **Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products** [16]. Further consideration is given to device components of combined products steering attention to mandatory fulfillment of essential requirements, compatibility of cellular and non-cellular components and the potential role of notified bodies within the evaluation process.

Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/ CHMP/GTWP/125459/2006) [17]
While the majority of described guidelines aims at providing recommendations and considerations on the complete development program of specific product groups this short guideline intends to define scientific principles focusing on non-clinical studies and to facilitate a harmonised approach within the EU. It is pointed out that the design of the study program needs to be made on a case-by-case basis and the relevance and adequacy of animal models used should be justified by the applicant. Studies are required to establish the following:

- pharmacodynamic “proof of concept” in non-clinical model(s)
- bio-distribution of the GTMP
- recommendation on initial dose and dose escalation scheme to be used in the proposed
  clinical trial
- identification of potential target organs of toxicity

- identification of potential target organs of biological activity (target tissue selectivity)
- identification of indices to be monitored in the proposed clinical trial
- identification of specific patient eligibility criteria

These points represent the minimal requirements and may be covered in an individual study program consisting of stand-alone and – where appropriate – combined studies in order to provide sufficient information for a proper first-in-man risk assessment.
Regarding specifically genetically-modified somatic cells special emphasis is again laid on bio-distribution, migration, persistence, differentiation, proliferation, immunogenicity and also on local tolerance. In case of cells that are encapsulated in biocompatible material during the manufacturing process, data supporting compatibility with the contained cells and the tissue at the site of implantation need to be provided. This also applies to data on stability of the encapsulation material in terms of degradation and unintended leakage and on benefits and risks of secretion of gene products.

Guideline of non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005) [18]
This guideline addresses the risk of germline transmission associated with the administration of gene transfer products such as naked DNA, genetically modified viruses, viral or non-viral vectors. Integrating and non-integrating vectors are defined and specified. Risk factors (dose levels, route of administration), likelihood assessment and possible non-clinical study designs and methodologic advice for testings are mentioned. A case-by-case decision is deemed appropriate and seeking scientific advice seems reasonable. In contrast, in genetically modified human cells the risk for inadvertent germline transmission is considered to be low and corresponding non-clinical studies are not recommended, unless otherwise justified, due to difficulties to be expected in case of animal testing of human cells.

Reflection paper on design modifications of gene therapy medicinal products during development (EMA/CAT/GTWP/44236/2009) [19]
In order to address the complicated regulatory situation in case of design modifications of GTMP during development the EMA published a reflection paper giving examples of potential significant changes (that are usually determined to serve an optimisation of the efficacy/safety profile) and consequences thereof. One example is the exchange of a promoter in genetically modified encapsulated cells that might be performed to increase the expression of the therapeutic protein. Due to scientific consequences of this step (new master cell bank, change of the capsule matrix) regulatory consequences such as a full adjusted toxicology program including exposure-related, impurity and biocompatibility testing need to be considered. This can happen by non-clinical bridging studies even if clinical trials are already ongoing. Seeking scientific advice is strongly recommended in any case.

2.1.3 Essential requirements for ATMP and integral medical devices: overview, intersections and ways of documentation

The previous section has demonstrated that the endeavour to achieve the development of a high-quality combined ATMP with an optimal benefit-risk ratio is facilitated by as well as depends on the permanent adherence to a large number of guidelines and other recommendations that are continuously revised according to current scientific knowledge and experience.
As pointed out in section 2.1.1, apart from the ATMP regulation (EC) No. 1394/2007, also Directive 2001/83/EC and Directive 93/42/EEC govern the developmental process of a combined ATMP consisting of a GTMP and a medical device. In the Annexes of these directives additional requirements regarding points to be considered during product studying and developing have been laid down. In Annex I, Part IV of Dir. 2001/83/EC requirements for ATMP, particularly for GTMP and sCTMP are outlined and need to be followed in addition to standard technical MAA provisions of Annex I, Part I. In Annex I of Dir. 93/42/EEC the essential requirements that have been mentioned in section 2.1.3 and that are applicable also or especially to medical device components of a combined ATMP are laid down.
The different requirements applicable to combined ATMP governed by Directive 2001/83/EC will be described in the following regarding crucial points, fields of intersection and suggestions for incorporation of respective information into the MAA documentation.

Annex I, Part IV of Dir. 2001/83/EC (MAA requirements for ATMP)
The risk-based approach is stressed as a tool determining the extent of quality, non-clinical and clinical data to be included in the MAA, in accordance with the scientific guidelines of section 2.1.2.1 and 2.1.2.2. After definition of GTMP and sCTMP Module 3, 4 and 5 requirements are outlined for both groups.
When a GTMP contains genetically modified cells, quality requirements of sCTMP also apply for this product. A description of the traceability system (chapter 3.1 of Annex I, Part IV) to ensure gapless surveillance of all substances involved regarding all steps from manufacturing to delivery of all substances involved needs to be provided. In case of genetically modified cells this includes the starting material consisting of the components used to obtain the cells, i.e. the starting and raw material to produce, prepare and preserve the vector and the cells (chapter 3.2.1.5 of Annex I, Part IV). Characteristics of the cells before and after genetic modification must be described (chapter 3.2.2 e) of Annex I, Part IV). Devices, which are combined with the ATMP and form an integral part of the product are also to be considered as starting material. Materials used during manufacturing such as culture media and growth factors are to be considered as raw material (chapter 3.3.1 of Annex I, Part IV). The traceability system needs to comply with the requirements established in Directive 2004/23/EC of the European Parliament and of the Council (Directive 2004/23/EC on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells).

GMP principles are to be followed in a verifiable way throughout manufacturing. Manufacturing steps are to be validated applying to the modified cells and the device. Potential impurities need to be addressed. In case other biological substances in addition to the modified cells are used their impact and interaction must be characterised.

Specific requirements for ATMP containing devices are focused on evidence of conformity of the medical device with the essential requirements mentioned above. Thereto belongs the description of physical characteristics, performance, product design as well as interaction and compatibility between cells and device (chapter 3.4.1 of Annex I, Part IV). As mentioned in section 2.1.2.1 any assessment performed by a notified body on the device should be provided.

In Module 4 the rationale for relevant animal species, models and *in vitro* testings addressing the specifities of the respective ATMP has to be discussed. Information on safety and efficacy regarding suitability and biocompatibility of all structural components needs to be provided. Specifically regarding GTMP, mandatory pharmacodynamics 'proof of concept' studies in relevant animal species and models have to be performed in order to demonstrate that the product resulting from genetic modification reaches its target and provides the intended function in a – where applicable – highly selective way. In terms of pharmacokinetics biodistribution studies addressing also the risk of germline transmission are needed. Single-dose toxicity research can be incorporated in such studies. Repeated-dose toxicity studies need to be considered also in case of intended single dosing resulting in a prolonged functionality of the DNA sequence within the human body. Study durations need to be adjusted accordingly. Integration studies are necessary for any GTMP. Genotoxicity, tumourigenic potential, reproductive and developmental toxicity and immunogenicity need to be investigated (chapter 4.1, 4.2, and 4.3 of Annex I, Part IV).

Regarding Module 5, specifities for ATMP consist of special circumstances arising in case of surgical procedures being necessary for application of the combined ATMP. Corresponding procedures need to be described and a definition of the required surgical expertise including the training plan of the physicians and a thorough description of the device should be provided. Safety and efficacy studies in case of combined ATMP have to be designed for and performed on the combined product as a whole. This includes dose-finding studies, efficacy studies with meaningful endpoints, long-term efficacy with special regard to long-term follow-up of safety and efficacy, which is to be included in the risk management plan. Safety studies should also cover a possible reassortment of existing genomic sequences and the potential for neoplastic proliferation due to insertional mutagenicity. In case of design modifications during clinical phase additional bridging studies to demonstrate comparability may be required. Pharmacokinetics and pharmacodynamics in humans include shedding and biodistribution studies and should intend to address expression and function of the DNA sequence after administration (chapter 5.1, 5.2, and 5.3 of Annex I, Part IV).

Any deviation from these requirements shall be scientifically justified in Module 2 of the dossier.

Annex I of Dir. 93/42/EEC (Essential requirements for medical devices)

The essential requirements applying to medical devices as stand-alone products and as integral parts of combined ATMP set emphasis on safety and performance of the device. The "design for patient safety" and the "design for lay, professional, disabled or other users" has to be established in such a way to optimise patients' and other users' health protection and to reduce the risk of use error regarding experience and technical knowledge of intended users.

The intended performance of the device must be ensured as far as possible and must not be negatively affected due to stress exposure of the device during normal conditions of use, transport or storage.

Risks of toxicity depending on the choice of used materials and the (bio-) compatibility between the materials and the modified cells and body fluids need to receive particular attention. Risks of degradation, unintended leaking and leaching of material components during (long-term) use have to be minimal.

Requirements (regarding applicability of legislation and involvement of competent authorities and their interactions) are also specified for cases when a device incorporates a medicinal product with an ancillary action to that of the device. Since the mode of action of the medicinal product part of the combined ATMP, for which the development scenario is to be outlined in the following sections, is the principal one, these provisions are not applicable. Still, interaction of competent stakeholders (EMA, notified body) can be achieved following specific procedures (reference is made to section 2.1.2.1) whenever useful and recommendable.

In case of intended use in special patient groups like children or pregnant or breastfeeding women this has to be justified specifically. In case of a combined ATMP a paediatric investigation plan has to be admitted at the end of clinical phase II at the latest.

Special emphasis is also laid on the elimination of the risk of microbial contamination of the device and consequential infection of the patient, users and others. Therefore easy handling of the device before and during surgical implantation needs to be considered during design. Devices intended to be delivered and applied under sterile conditions must be designed, manufactured and packed accordingly. Their ergonomic and technical features need to be established in such a way that the risk of device damage and user/patient injury is minimised and that reasonably foreseeable environmental conditions like magnetic fields, external electrical influences, electrostatic discharge, pressure or temperature do not affect the safety and performance of the device in a relevant way.

The last section of requirements laid down in Annex I of Dir. 93/42/EEC focuses on instructions for use to be provided by the manufacturer in order to ensure application of the device according to the intended use. Provisions are laid down as to the location (outer packaging, leaflet) and form (symbols, colours where appropriate) of those instructions. Labelling information such as batch / re-use or single use / date of expiry / sterilization procedure / storage conditions / handling conditions / performance / risks and precautions / package content / contained medicinal product should be present where appropriate and practicable.

According to the Annex demonstration of conformity with the essential requirements must include a clinical evaluation in accordance with Annex X of Directive 93/42/EEC. This,

however, only applies to medical devices governed by this directive. Devices being components of a combined ATMP (the ATMP part exerting the principal mode of action) and thus being governed by Directive 2001/83/EC have to demonstrate compliance with these essential requirements within the frame of the CTD MAA dossier or/and within the results of a notified body assessment if available. Corresponding Meddev guidelines on the compilation of a clinical evaluation or on borderline and drug-delivery products incorporating an ancillary medicinal substance do therefore not apply to the combined ATMP to be discussed.

It is the manufacturer's responsibility to comply with the essential requirements in a credible and reproducible way. Regarding innovative combined products this often happens by his own means. For some parts of the product or the manufacturing process, however, technical or other specifications may be applicable, especially when they have been prepared by the European standards organisations (e.g. CEN, CENELEC) on behalf of the Commission (harmonised standards according to Article 5 Dir. 93/42/EEC). They serve not only as scientific and technical support but also as an assurance of compliance for the manufacturer. Applicable standards might be such concerning the quality management system of medical devices (ISO 13485), sterilization of healthcare products (e.g. ISO 14937), biological evaluation of medical devices (ISO 10993) or clinical investigation of medical devices (ISO 14155).

Intersections and suggestions for MAA documentation

The requirements governing both ATMP and Medical devices obviously set their emphasis on safety aspects, which determine largely the quality testing and the non-clinical and clinical study program. Details on clinical safety aspects of the whole product, also after marketing, have to be provided in the risk management plan. During preceding development including non-clinical and early clinical phase, however, a thorough risk profiling is fundamental to the investigations needed for the product. This includes any risk factors emerging due to the characteristics of the medical device. Moreover, evidence has to be provided in the MAA documentation that the combined ATMP complies with the essential requirements regarding the device part. All this information has to be presented in the MAA dossier in a meaningful way.

A quality- as well as toxicology-related issue stressed in both Annexes is the compatibility of the device part with its environment (body fluids, tissue) with the medicinal part of the whole product i.e. the genetically modified cells. Physical and biological characteristics of the device determining its compatibility with the environment and other components may be linked to the overall manufacturing process as well as to its development and corresponding controls. Thus information in this regard may be included in the part describing the composition of the product with the components' chosen materials and in the pharmaceutical development (of the whole product) part of Module 3 with references to Module 4 and 5 when appropriate. Affection through normal storage conditions should be covered by the stability section and sterilisation procedures of the device and the whole product should be documented in the manufacturing and container closure system part of Module 3.

When it comes to testings regarding possible effects of biocompatibility limitations on the performance and safety of the product this should be demonstrated in the respective parts of Module 4 (e.g. long-term toxicity, impurities, immunotoxicity, genotoxicity, carcinogenicity) with reference to Module 5 when appropriate. When evaluating the need for specific biocompatibility studies, recommendations contained in the International Standard ISO-10993 ("Biological Evaluation of Medical Devices Part 1: Evaluation and Testing") are advised to be considered to achieve a sound biological evaluation, which supports the toxicological profile of the whole product to be outlined in Module 4.
When, in accordance with the essential requirements for medical devices, the risk for possible microbial contamination of the device is studied, generated data also need to be incorporated in the toxicity sections of Module 4.
Additional studies investigating the behavior of the device under reasonably foreseeable environmental conditions like mechanic stress, magnetic fields, external electrical influences, electrostatic discharge, pressure or temperature should be incorporated in the section describing other toxicity studies like e.g. mechanistic studies.
In all cases corresponding adverse events during clinical administration have to be documented in the safety/efficacy sections of Module 5.
Overall performance of the device can be incorporated in an appropriate way in the pharmacology section of Module 4 and in the efficacy section of Module 5.
The essential requirements also demand the best possible elimination of the risk of use error. In case of an implantable device containing a GTMP this may go hand in hand with the 2001/83/EC requirement to describe the surgical procedure needed for administration of the combined ATMP including required expertise and experience of the executing physician. This information has to be incorporated e.g. at the beginning of the safety section in Module 5.
If the product is designed to undergo sterilisation before delivery and application the consequence of possible damage to the sterile packaging needs to be outlined in the safety part of Module 5 describing contraindications or precautions.
In case of intended use of the device and consequently of the whole product in special patient groups like children or pregnant or breastfeeding women corresponding evidence has to be provided in the efficacy/safety section of CTD Module 5.
Instructions for use as required for the device part need to be incorporated in the labelling of the whole product.
Additional information like e.g. the assessment of a notified body on the device part – if available – may be practical to be presented along with the MAA in a separate or annexed manner.

2.1.4 Particularities valid for micro, small and medium-sized enterprises (SME)

As indicated in section 2.1, in many cases innovative developments of advanced therapies are initiated by micro, small and medium-sized enterprises (SME). In view of the immense costs of ATMP development assumingly sometimes exceeding those of chemical medicinal products and the required highly specialised regulatory expertise, which often goes beyond the capacities of SME, the EMA has established the so-called SME office that

dedicates itself to the promotion of the development of new medicines by SME. Incentives in the form of regulatory and administrative assistance, organisation of workshops and training sessions, fee reductions (e.g. for scientific advice/protocol assistance, inspections, MAA, post-authorisation activities, scientific services, establishment of maximum residue limits for veterinary products, MedDRA license), assistance with translation of the product information and inclusion in the public SME register have been set up.
Commission Recommendation 2003/361/EC defines micro, small and medium-sized enterprises and has to be considered when eligibility is determined.
Commission Regulation (EC) No 2049/2005 lays down rules regarding the payment of fees to, and the receipt of administrative assistance from the EMA by SME.

As demanded by the ATMP regulation and introduced through implementing Regulation (EC) No 668/2009 one of the incentives for SME is a specifically reserved certification procedure concerning quality and non-clinical data, which happens independently from MAA. The corresponding guideline and procedural advice ([3], [4]) have been described earlier in section 2.1.2.1. The certification procedure is intended to provide developmental guidance and support concerning available quality and non-clinical data whereas advice for future development and benefit-risk assessment remains reserved for pre-submission protocol assistance procedures and the evaluation of MAA.

An extensive **user guide** entitled '**Addressing the needs of small and medium sized enterprises**' [20] has been published by the EMA with the last version having been revised in August 2014.
It describes the SME initiative, the classification procedure for ATMP and the Scientific Advice procedure, tries to cover the phases of medicinal product development of human and veterinary products and outlines the centralised marketing authorisation procedure.

3 Presentation of a fictitious combined ATMP under development

This section presents the combined ATMP, the non-clinical and early clinical development of which is about to be outlined in this thesis, and the disease, which is intended to be treated with the product.
Achromatopsia, a severe form of complete color blindness, has been chosen as the target disease. The eye disorder is an inherited retinal disease, which is transmitted autosomal-recessively.
The disorder is quite rare. In Germany approximately 3,000 and in the United States approximately 10,000 people are believed to suffer from achromatopsia. Patients with complete or almost complete achromatopsia are not only limited by the absence of color vision but also have reduced visual acuity (amblyopia), nystagmus and severe photophobia, which makes them practically blind in sunlight (hemeralopia). Common daily activities like reading, computer work or driving may be impaired, which presents a high level of disability. No treatment for a complete cure of achromatopsia is currently available and despite a number of non-clinical investigations no clinical trials have been performed or are currently open for enrolment.

At present, mutations in six genes have been discovered by different research groups around the world and in different populations. Current scientific knowledge assumes the disease to be caused by a monogenetic defect. Most known mutations ultimately lead to dysfunction and failure of signal transduction (e.g. through defective ion channels or impaired activity of catalyzing enzymes) on the level of the retinal cone photoreceptors. However, not all molecular mechanisms influenced by the gene defects are fully understood. Recently a research group has discovered a new mutation in several families of different ethnic backgrounds affecting the unfolded protein response (UPR), a ubiquitous and important cellular repair system (Kohl 2015). The affected gene ATF6 usually encodes the expression of activating transcription factor 6, a key regulator of UPR and cellular endoplasmic reticulum (ER) homeostasis.

The combined ATMP product under non-clinical and early clinical development intends to offer a long-term therapeutic option for patients with this genetic defect.
The product shall consist of a medical device in form of an encapsulated cell technology (Yasukawa 2010) that is designed to be implanted into the vitreous body cavity of the eye in a surgical procedure. Fixation of the device at the pars plana should be done by means of biodegradable sutures. The device measures only few millimeters in length and width. Cells encapsulated within the device are human allogeneic fibroblasts, which are genetically modified through *in vitro* manipulation. The desired DNA sequence is isolated from healthy humans and multiplied by polymerase chain reaction. It then receives a liposome coating (intended as a non-viral vector) forming an appropriately sized cationic lipoplex before being transfected into the fibroblasts in an electroporation procedure or via endocytosis. Resulting cells, the nucleus of which has incorporated the DNA, are cultured on cell banks for an appropriate period of time before their transfer into the device. Within the medical device the cells are intended to permanently produce and secrete ATF6, which diffuses into the vitreous via a semi-permeable hollow fiber membrane. The membrane envelops the cells, allows influx of nutrients and oxygen and separates them from cellular and molecular elements of the immune system. After release of the transcription factor into the vitreous body it diffuses through the organic hydrogel to the posterior part of the eye where it develops its therapeutic action at the retinal cone photoreceptors. The combined product is designed in such a way that the cells producing the therapeutic protein are likely to survive and be therapeutically active for several months. In case of need for removal of the product surgery is necessary.
The product under development is thus a combined ATMP consisting of a somatic gene therapy exerting the principal therapeutic effect and represented by genetically modified human allogeneic fibroblasts, which are connected with and incorporated into a capsule-like technology serving as an implantable non-biodegradable drug delivery device.

4 Description of a development scenario

4.1 Procedural and regulatory steps

The following procedural recommendations do not have to be performed in the exact order as described. Corresponding regulatory processes may just as well take place in parallel to each other or on a repeated basis, depending on in how far they are applicable and appropriate.

4.1.1 SME status and implications thereof

4.1.1.1 SME registration

Early – if not initial – considerations should be given to the question in how far the developing biopharmaceutical company is eligible for SME status according to Commission Regulation (EC) No 2049/2005 (reference is made to section 2.1.4). A survey performed by the EMA, published in 2011 (EMA/733642/2011) (EMA webpage) revealed that up to that point in time the majority of respondents (77%) indicated that they were aware of the agency's SME programme, 50% "to some extent" and 27% "to a great extent". The vast majority of those who disposed of detailed knowledge concerning the programme rated the registration process as either very "good" or "good". Yet there was articulated an ongoing need for increasing detailed awareness of the programme including the financial instruments and funding opportunities available. Additionally more information and advice with regard to administrative challenges (capable of unnecessarily prolonging a development process) as well as improved training and regulatory assistance are considered crucial elements. A more proactive approach from the regulators' side is also demanded – on the basis of an analysis of the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database aiming at identifying the major stakeholders of ATMP development – in a publication by Maciulaitis (2012) in order to provide important assistance such as scientific advice, briefing meetings with the EMA Innovation Task Force or ATMP classification and certification. Regulators should to a higher extent encourage direct interaction between biopharmaceutical companies and regulators. This appears to be a key predictor of successful development.

Having such considerations in mind the company should seek early contact with the SME office of the EMA and complete and submit the application form "Declaration on the qualification of an enterprise as a micro, small or medium-sized enterprise (SME)". On the basis of recent annual accounts, information on ownership and proof of establishment in the EEA the EMA will issue an EMA-SME number and assign SME status. The fulfillment of certain criteria fixed in the SME User Guide [20] and in the annex of the European Commission Recommendation 2003/361/EC is prerequisite for the registration process. The criteria consist of three main thresholds being (A) staff headcount, (B) annual turnover and (C) annual balance sheet. Once the assignment has been completed successfully the company has access to a number of incentives, some of which will be described in the following. Generally speaking, they consist of noticeable fee reductions,

translation of regulatory documents (both specified in Commission regulation (EC) No 2049/2005), scientific and regulatory assistance and advice, workshops and training as well as inclusion in the public SME register. To maintain the SME status, the company has to submit a completed declaration annually, based on its most recent accounts.

4.1.1.2 Innovation Task Force (ITF) Briefing Meeting

A promising tool for establishing an early and relatively informal dialogue with multidisciplinary expert groups with scientific, regulatory and legal competences is to apply for an ITF Briefing Meeting at EMA. The meetings, which are arranged within 60 days of receipt of request, are free of charge and generally intend to facilitate exchange of information, provide guidance in the development process and complement and reinforce formal regulatory procedures such as ATMP classification and certification, designation of orphan medicinal products and scientific advice. The request form along with a detailed standard operating procedure can be found on the EMA webpage.
The ITF describes its objects in a way that make clear their potential key role within the development process. Possibly based on the experience of frequent failures in the ATMP field, also due to "regulatory complexities" (as stated by Maciulaitis et al.), the task force wants to

- "proactively identify scientific, legal and regulatory issues of emerging therapies and technologies;"
- "address the impact of emerging therapies and technologies on current scientific, legal and regulatory requirements" with the Agency's expert units;
- thus "identify the need for specialized expertise at an early stage" (EMA webpage)
- provide early advice on classification and demarcation (for borderline products).

As already stated in section 1 every emerging ATMP requires a specifically tailored development program, the determination of which necessitates profound and farsighted expertise in order to avoid failure. The ITF initiative intends to be a first or accompanying step on the way to innovative therapies of diseases representing an unmet medical need.

4.1.1.3 Classification of the combined ATMP

As mentioned in section 2.1.2.1 the classification and assignment, respectively, of the product under development represents another regulatory step to be taken by the applicant as early as possible and before the steps to be described in the following sections. This procedure is optional, yet highly recommendable for enterprises with limited regulatory capacities and is, of course, not reserved for SME only. Still, it will be presented at this point due to its essential role and the implications it entails for SME.
Apart from the company the CAT (as scientific instance), the EMA Secretariat (coordination), the European Commission (as an instance to be consulted on scientific and regulatory issues) and other scientific committees and working parties are involved in the procedure. An application has to be filed at least 15 days before start of procedure and according to fixed submission dates to the CAT Secretariat, which appoints the EMA Coordinator. Within the application information on the product (active substance, finished

product, mechanism of action, summary of the status of development) has to be submitted for the EMA Coordinator to check if the product complies with the ATMP claim. The thereafter following 60-day CAT procedure for ATMP classification can be found in detail in the Procedural advice document [1]. Possibly there is inserted a clock stop after Day 30 in case more information is needed. In the end the CAT scientific recommendation is sent to the applicant and a summary is published on the EMA webpage.

It is important that the briefing information initially provided by the applicant contains meaningful and conclusive facts that allow the working parties to perform a sound classification of the product based on its components (genetically modified cells, viability of cells, delivery device etc.), the proposed use of its components (mechanism, location, synergism, applicability of GTMP/sCTMP/TEP definitions etc.) and the finished product (connection of components etc.). For the product in question specifically three legal provisions of Regulation (EC) No 1394/2007 apply and will again be stressed here:

- aforementioned Article 2(1): "A 'Combined advanced therapy medicinal products' means an ATMP that fulfills the following conditions: it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC (…), and its cellular or tissue part must contain viable cells or tissues, (…)."
- Article 2(2) with regards to products containing cells or tissues: "Where a product contains viable cells or tissues, the pharmacological, immunological or metabolic action of those cells or tissues shall be considered as the principal mode of action of the product."
- the demarcation rule between ATMP in Article 2(4) and 2(5): "(…) A product which may fall within the definition of a sCTMP or a TEP, and an GTMP, shall be considered as a GTMP."

To illustrate the considerations involved in a possible classification scenario the decision trees for GTMP (including combined ATMP) and for sCTMP and TEP (including the demarcation to GTMP) are shown in Fig. 1 and Fig 2, respectively (reference is made to the reflection paper on classification of ATMP [2]).

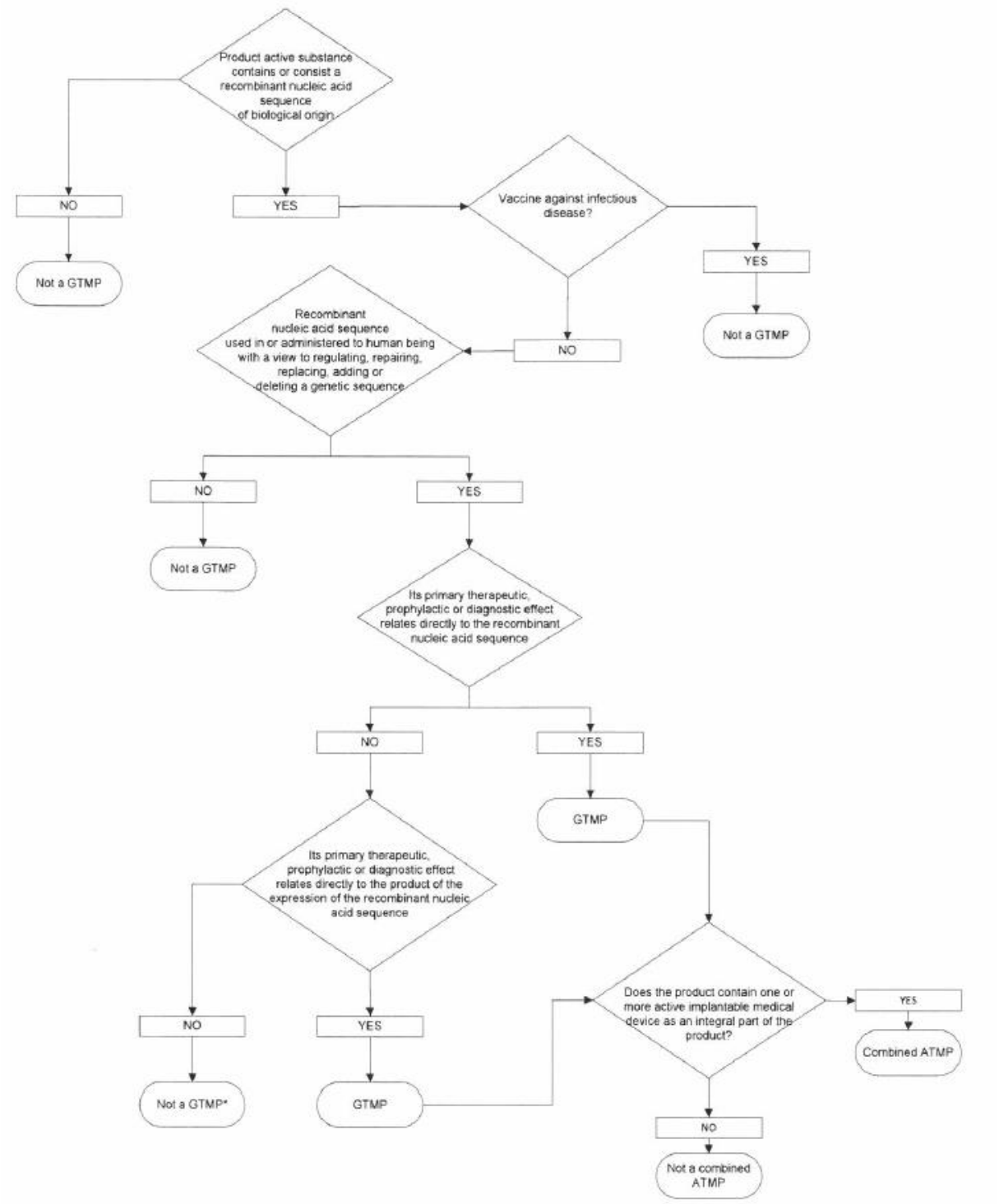

Fig. 1: Decision tree for GTMP [2]

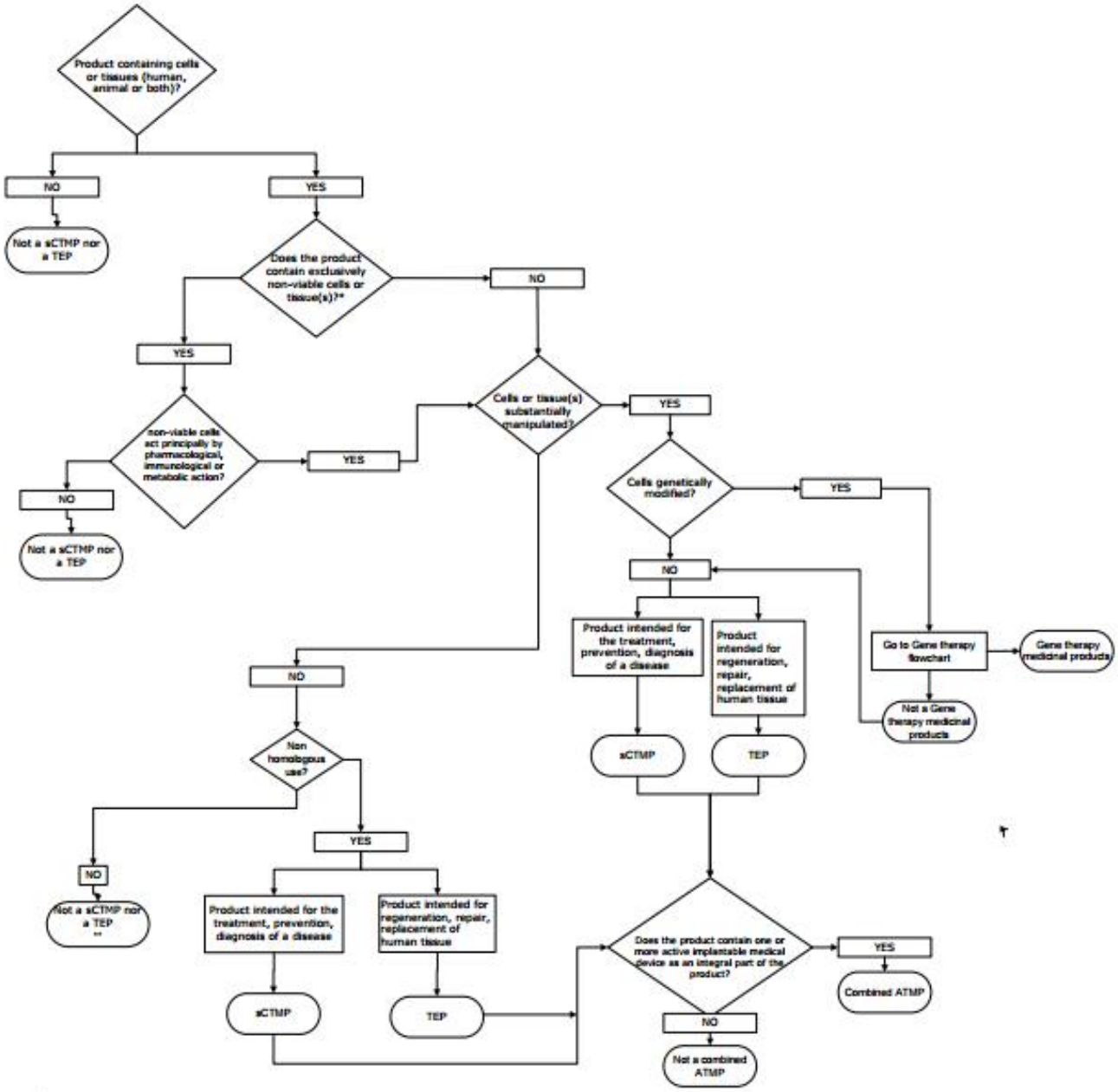

Fig. 2: Decision tree for sCTMP and TEP [2]

4.1.1.4 Certification of the combined ATMP

Another central SME incentive is the evaluation and certification of already generated scientific data as a stand-alone, not legally binding evaluation procedure in order to provide a timely "snapshot" to the company regarding the compliance of the so far completed studies with relevant scientific and technical requirements set out in Annex I of Directive 2001/83/EC and with state-of-the-art scientific standards and guidelines.
At the time of expressing intention to make use of the certification procedure it is expected -unless otherwise justified - that a classification of the product has already been performed. Additionally the intended clinical use and a corresponding risk analysis should be available although clinical studies are not part of the certification procedure. To reach certification, a subset of quality data and non-clinical data is required, which should be presented in the format of the Common Technical Document (EU-CTD). With regard to quality data, information related to the starting and raw materials, manufacturing process of the active substance, its characterisation, control, description and composition of the finished combined ATMP has to be provided. Information on the device part of the product needs to be incorporated in module 3.2.R of the CTD (e.g. results of the assessment of the medical device by a notified body) in the "medical device" section. Detailed instructions on the minimum content of Module 3 (and 2.3) are given in the respective guideline [3] (see also section 2.1.2.1) and will not be discussed in detail here. With regard to non-clinical data at least primary pharmacodynamic data (*in vitro* and at least one *in vivo* study in a relevant animal model) supporting the rationale for therapeutic use, pharmacokinetics, biodistribution data and at least one toxicity study should be submitted. Further non-clinical proof-of-concept pharmacology studies will be considered supportive without being part of the formal certification – same as risk analysis outcome and clinical data, which should be incorporated into Module 2.2. A non-clinical overview for justification of the non-clinical development should be submitted.
It is noted that only final study reports will be accepted for certification. Additionally the applicant should point out in how far studies are submitted for certification or merely for support of the data to be certified.

In the Procedural advice document [4] (see also section 2.1.2.1), which refers to the guideline, the "optimum time point to apply for the certification procedure is when the ATMP has reached a level of sufficient development with respect to quality and non-clinical data". It should be noted that a certification procedure can be applied for more than once. In such a case it is crucial that the complete dataset (including data already certified) is submitted. The procedural advice document describes the certification process in great detail starting from pre-submission activities. The applicant has to inform the EMA of his intention to submit an application for certification at least 70 days (Day -70) before submission/start of procedure (specifying the intended submission date, product-related background information, type of data, stage of development) using the appropriate template for the "pre-submission request form" available on the EMA webpage. Relevant attachments are SME status confirmation, aforementioned background information, information on the status of the medical device part (i.e. declaration that the device meets

the essential requirements laid down in Directive 93/42/EEC (see also section 2.1.3) and a table of content for Module 3 and 4. Submission has to take place according to the dates published on the EMA webpage. During the following period eligibility is checked and a CAT and an EMA Coordinator are appointed (before Day -59). A pre-submission meeting possibly takes place between Day -40 and -20. Approximately on Day -50 a draft certification application dossier should be submitted to EMA and CAT for pre-validation and identification of additional expertise needed. Until Day -10 the final certification dossier - amended accordingly - should be received by EMA. After validation it should be sent to the CAT Coordinator, the CAT peer reviewers and to all CAT members if required. Regarding the content of the complete application package reference is made to the procedural advice document.

During the first 40 days of the procedure an evaluation report is prepared by the CAT Coordinator and distributed to other CAT members and the EMA. The possible need of a site visit or/and an oral/written clarification by the applicant is substantiated in this report. In case of the first, the procedure is suspended until the site visit report is made available to EMA and CAT. In case of the latter, a clock stop from Day 60 (lasting either 30 or 60 days) takes place for preparation. For these two scenarios reference is made to the procedural advice document. If no additional explanation is deemed necessary the applicant receives the consolidated certification evaluation report by Day 75. By Day 95 EMA issues the certificate (positive opinion) or an advisory letter (negative opinion) and forwards the adopted documents to the applicant.

The timeline is outlined in Figure 3 [4].

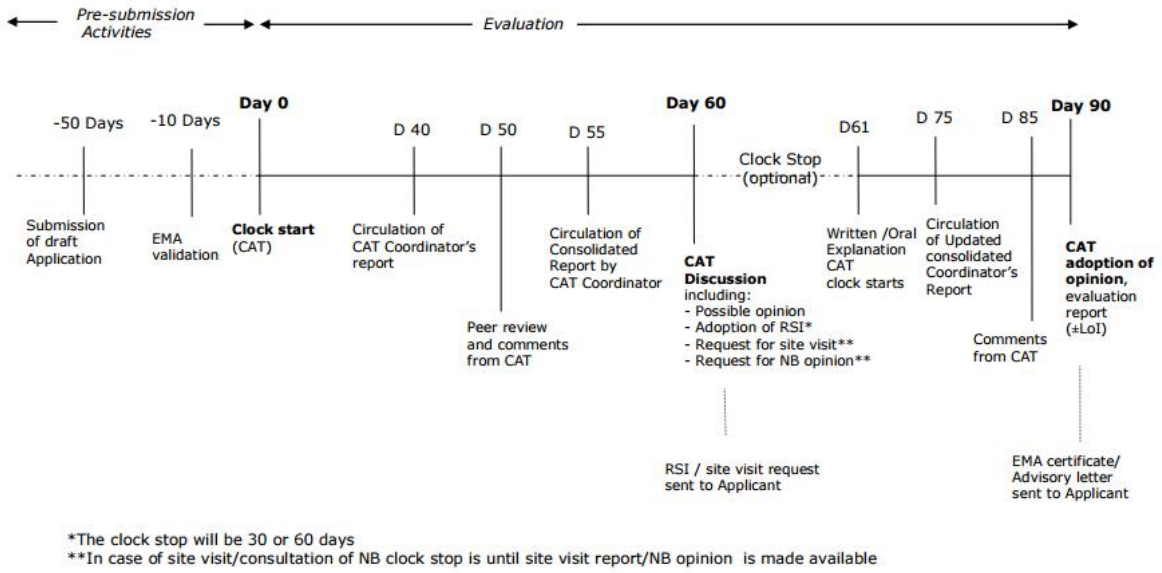

Fig. 3: Timeline of the certification procedure for (combined) ATMP [4]

4.1.1.5 Involvement of a Notified body for evaluation of the combined ATMP

As indicated in the description of the certification procedure (see 2.1.2.1 and 2.1.4) the applicant may wish information on the status of the medical device part of the product to be included in the certification dossier. If such information, i.e. a declaration of a relevant Notified body that the product complies with the essential requirements described in section 2.1.3, is available it has to be incorporated into the relevant CTD section. The EMA may ask the relevant Notified body to transmit any information related to the result of the assessment. The Notified body should provide this information within one month.
If no assessment (and Notified body) is available one out of two options can be persued.
Either the conformity check of the device part with the essential requirements is temporarily excluded from the evaluation and the certificate and may be performed in a later certification procedure when it is available or (at the latest) during evaluation of marketing authorisation application. Or a relevant Notified body is consulted (reference is made to section 2.1.2.1) if the CAT, which is advised by its experts for medical devices, deems such an involvement necessary. In such a case the procedure is suspended for the duration of the collaboration process. The EMA Secretariat coordinates communication and exchange of information between the CAT, CHMP and the Notified body (members of the Collaboration Group). In general it might be of interest for the applying company that the CAT primarily interacts with the Notified body. However, any interaction will usually be done in conjunction with the applicant. This also applies to the identification of a relevant Notified body. Additionally, the applicant will be responsible for any fee payment directly to the Notified body for the work performed.
It is the responsibility of the applicant to provide any available information on the medical device part i.e. relevant studies capable of supporting that the device fulfills the essential requirements. As pointed out in section 2.1.3 emphasis is laid on safety and performance of the medical device. Therefore the focus of the consultation may lie on potential effects of the combination of the two components on the performance of the device part with regard to its original technical, clinical and biological characteristics. The information required from the applicant may thus include a description of data concerning the interaction and compatibility between genes, cells, (ophthalmological) tissue and the structural device components. Other potential issues requiring the provision of distinct data (e.g. with regard to other aspects of toxicity, unintended degradation, leaking, leaching or microbial contamination) can be found in section 2.1.3 (Annex I of Dir. 93/42/EEC - Essential requirements for medical devices), in corresponding scientific guidelines (reference is made to section 2.1.2.1 and 2.1.2.2, e.g. guidelines [3], [8], [13], [15]) and in section 4.2.1.
The cooperation scheme involving EMA, CAT, a potentially involved Notified body and the pharmaceutical company is shown in Figure 4.

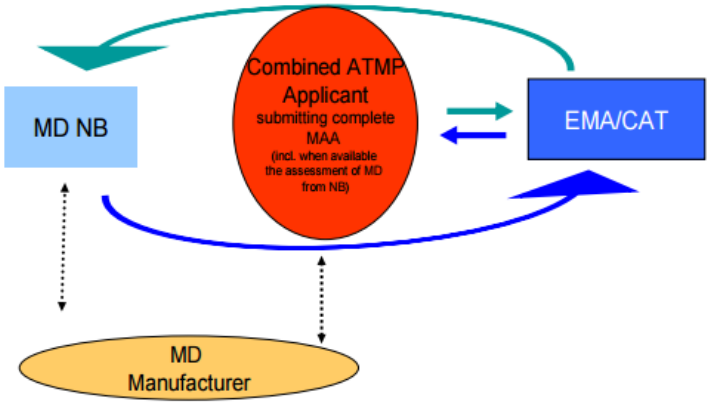

Fig. 4: Cooperation scheme involving EMA, CAT, and a Notified body [7]

4.1.2 Other important regulatory procedures

The following regulatory procedures play key roles in the developmental process of almost every innovative medicinal product but are not specifically and necessarily linked to combined ATMP. Due to their importance they will be mentioned here briefly with reference to corresponding guidance documents and legal provisions.

4.1.2.1 Scientific Advice and Protocol Assistance

Apart from the possibilities largely reserved for SME to seek relatively informal advice from the EMA and its associated committees, the official Scientific Advice (SA) or Protocol Assistance in case of designated orphan medicinal products is a formal way of gaining not legally binding prospective support in the connected fields of regulatory and scientific issues. SA can be considered as key element in order to establish and validate the project-specific strategy of development. That is, SA can be sought at any time during development, in the case of a complex combined ATMP it is highly recommended to do so as early as possible. For the product in question it is reasonable to make corresponding efforts as soon as the product has undergone the classification procedure (see 4.1.1.3) in order to reach assurance concerning the generation of non-clinical and quality data that are proper for certification. In general it is highly recommended for the applicant to seek SA at every major development milestone (entering of non-clinical phase, planning of adequate animal models, considering adequate tests for fulfilment of medical device essential requirements, planning of clinical phase etc.). The duty of the competent authority to provide SA has been fixed legally in Article 57(1)(n) of Regulation (EC) 726/2004 or in Article 6 of the Regulation on Orphan Medicinal Products (EC) 141/2000. The CHMP has solely for this reason established the Scientific Advice Working Party (SAWP), which is a multidisciplinary expert group and liaises with other working parties and committees if necessary.
For the applicant it is important and helpful to carefully establish a timeline that fits his plan of development and his resources. The SA (application) procedure always includes a

pre-submission phase starting with a Letter of Intent and the submission of an official request according to fixed timelines. If considered necessary a pre-submission meeting is held (determining the duration of the pre-submission phase to be either 30 or 60 days). The actual SA procedure takes either 40 or 70 days depending on the necessity of a face-to-face meeting with EMA. The procedure is shown graphically in Figure 5.

It is of special importance for the applicant to stay in close contact with the procedure-specific designated coordinator, who is appointed after EMA's receipt of the Letter of Intent and who is the applicant's key contact. A specific, precise and well-structured list of questions (LoQ) concerning the issues to be discussed and the applicant's position and a well-prepared, tailored-to-the-LoQ and up-to-date data briefing package substantiating the applicant's positions need to be submitted with the request.

If the SME status of the company is properly registered (reference is made to section 4.1.1.1) no separate fee reduction request is necessary but will be initiated internally by EMA.

Further details about SA and special forms thereof (e.g. parallel EMA/FDA SA or parallel SA from EMA and health technology assessment bodies) can be found on the EMA webpage and in the guideline "European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance" (EMA/691788/2010 Rev. 7) [21].

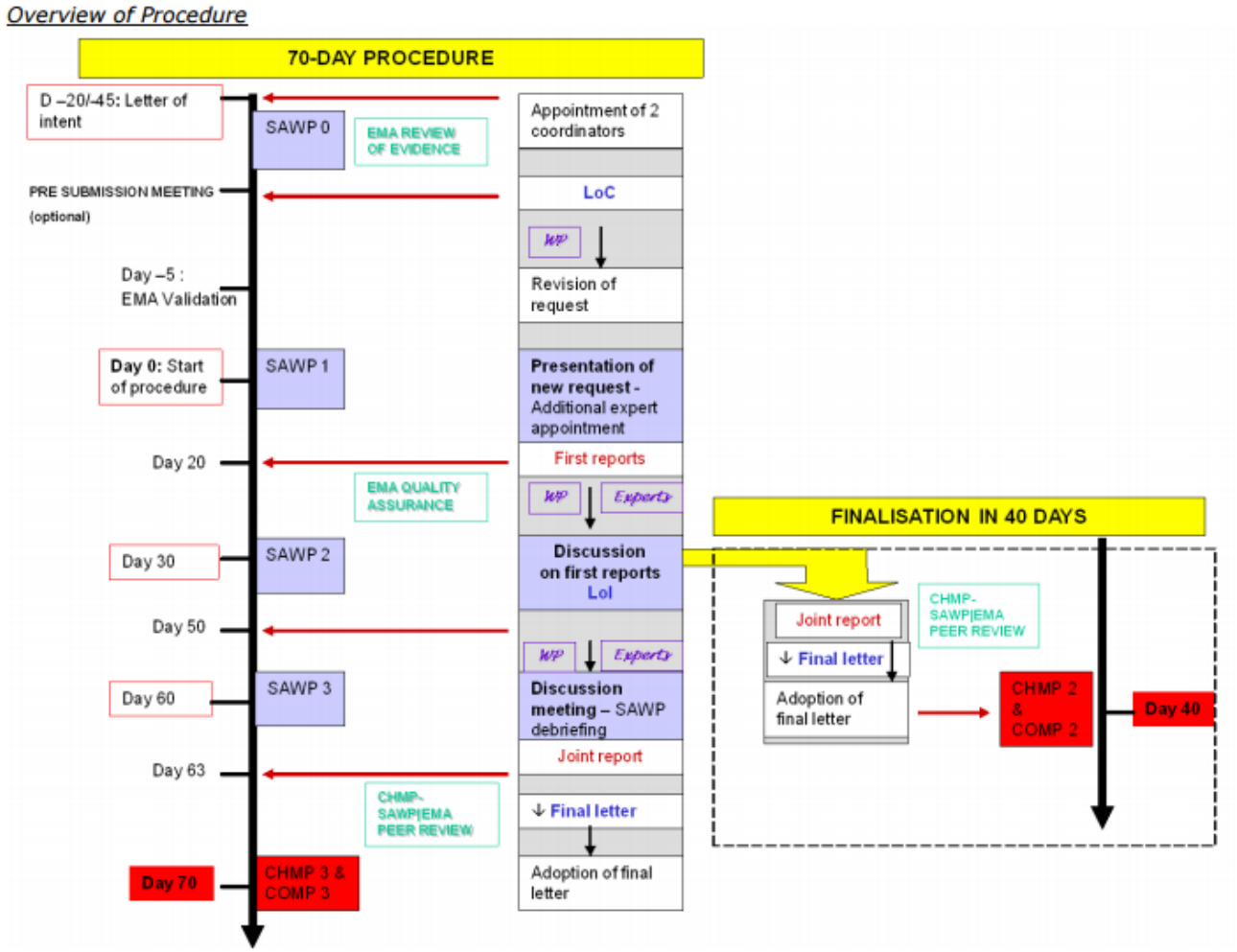

Fig.5: Overview of the procedure concerning Scientific Advice and/or Protocol Assistance [21]

4.1.2.2 Orphan drug designation

ATMP are most often developed for the treatment of rare diseases representing an up till then unmet medical need. This can be considered the case for the combined ATMP in question. Legally based on the Regulation (EC) No 141/2000 of the European Parliament and of the Council on Orphan medicinal products and on the Commission Regulation (EC) No 847/2000 determining the criteria for designation of a medicinal product as an orphan medicinal product, the corresponding status along with a number of incentives (protocol assistance, market exclusivity of 10 years, fee reductions) has been established aiming at facilitating development and market access for products that treat a medically plausible condition in humans

- which is life-threatening or debilitating
- which has a prevalence of not more than 5 in 10,000 or which is unlikely to generate sufficient return on investment
- for which no satisfactory methods or medicinal products exist or – in case there do – which will be of significant benefit.

Regarding the application procedure the applicant has to notify the EMA of his corresponding intentions at least 2 months prior to submission. Also here a pre-submission meeting is strongly recommended. Application is free of charge and must be made using the respective EMA forms. Parallel application with international regulators, e.g. USA and Japan, is possible. Two EU countries will be assigned as coordinators, who prepare and circulate a summary report to the Committee for Orphan Medicinal Products (COMP) established by the EMA. Circulation of the report, discussion and adoption by the COMP usually happens until 90 days after application submission and final decision is taken by the Commission within another 30 days.
Detailed procedural guidance (guideline document EMA/710915/2009 Rev. 13 [22]) and information on current submission deadlines and relevant sources for orphan disease prevalence data (EMA document EMA/452415/2012 Rev. 1 [23]) can be found on the EMA webpage.

4.1.2.3 Clinical Trial Authorisation

Entering clinical phase with a combined ATMP represents a broad range of specific challenges to the sponsor, which require profound and farsighted scientific and regulatory preparation, involving multidisciplinary expertise. Due to the high variety of demands to be met only regulatory cornerstones to be considered unconditionally will be outlined in this section. At the same time, it is pointed out that the involvement of a sufficiently qualified Clinical research organisation (CRO) might be indispensable for an SME with limited capacities and experience.
The European legal framework for planning, applying for and performing a clinical trial is represented by Clinical Trials Directive 2001/20/EC, which will be replaced by the new Clinical Trials Regulation 536/2014 coming into force in June 2016 at the earliest. There will be a transition period of 3 years, after which Reg. 536/2014 will be the sole Clinical

Trials legislation. Up until then the objectives of Dir. 2001/20/EC, namely the protection of clinical trial subjects, the assurance of compliance with GCP, and the definition of Europe-wide harmonised procedures for involved stakeholders are covered by a number of principles to be implemented in national legislation. The most important ones are

- definition of responsibilities of the sponsor
- need for EudraCT number (to be obtained before CTA application from the EudraCT Community CT System)
- compilation of an Investigational medicinal product dossier (IMPD) and Investigator's brochure (IB)
- procedures of application for clinical trial authorisation (CTA) and Ethics committee's (EC) review
- definition of GCP-standards and GMP-requirements (also laid down in Dir. 2005/28/EC and Dir. 2003/94/EC, respectively) and corresponding inspection procedures
- pharmacovigilance requirements
- definition of trial subject and data protection rules
- notification of substantial amendments and end-of-trial

The Directive's implementation in German national law is most prominently represented by §§40-42b AMG, the GCP-Verordnung and the AMWHV (Verordnung über die Anwendung der Guten Herstellungspraxis bei der Herstellung von Arzneimitteln und Wirkstoffen und über die Anwendung der Guten fachlichen Praxis bei der Herstellung von Produkten menschlicher Herkunft - Arzneimittel- und Wirkstoffherstellungsverordnung). On a national basis the Paul-Ehrlich-Institut is responsible for evaluation and approval of CTA for trials with (combined) ATMP/GTMP to be carried out in Germany.

As mentioned in section 4.1.2.1 it is highly recommended seeking scientific and procedural/regulatory advice from the authorities at this crucial point of development and before submission of a CTA. In EudraLex – Volume 10 associated guidelines and recommendations can be found covering large parts of the principles listed above.

In general, it is possible to submit the applications for CTA and the Ethics committee's (EC) review procedure in parallel. In each member state where trials are to be performed a CTA and a favourable EC opinion need to be achieved. Depending on the complexity of the product and on the need for external consultation (e.g. notified bodies, scientific advisors for GTMP), approval periods of the competent authority (CA) starting after the validation period vary between 90 and 180 days resulting, in favourable cases, in an explicit approval for CT performance with the combined ATMP. However, the sponsor needs CTA and a favourable EC opinion to be allowed to start a trial. Dir. 2001/20/EC demands the same approval periods from national ECs as from CAs. The applicant/sponsor should know that these institutions do not always coincide completely regarding their opinions and that it falls within the sponsor's responsibility to integrate possibly differing requests.

The Clinical Trials Facilitation Group (CTFG) established by the Heads of Medicines Agencies (HMA) does not liaise with the Ethics Committees either but offers a voluntary harmonisation procedure (VHP), within which national assessors are meant to come to an agreed approval recommendation to be circulated to the national CAs of respective trial

sites, in order to accelerate CTA. Regarding the still rather divergent practices in the different member states when it comes to approval procedures, requesting for VHP is deemed very worthwhile, in case the applicant wishes to perform a multi-national clinical investigation.

4.1.2.4 Paediatric Investigation Plan (PIP)

The applicant also needs to be aware of and prepare for the necessity to submit a PIP during development of the combined ATMP. Due to the fact that achromatopsia, the disease to be treated by the product in question, cannot be declared as a condition never affecting children, the product will fall under the scope of the paediatric regulation and associated guidelines/recommendations. The legal provisions and emerging procedural consequences for the process of development will only be outlined briefly in this context because PIP submission is usually not relevant before the end of early clinical phase in adults and, as experience has shown, even tends to be further postponed by means of deferrals in many cases until the pre-MAA adult data set is (almost) complete. Nevertheless, it is recommended to integrate considerations of paediatric drug administration already in nonclinical development stages, e.g. in form of juvenile animal studies (reference is made to the guideline on the "need for nonclinical testing in juvenile animals of pharmaceuticals for paediatric indications" - EMEA/CHMP/SWP/169215/2005 [24]).

The Regulation (EC) 1901/2006 lays down the main criteria regarding involvement of paediatric drug development. In line with this regulation the Paediatric Committee (PDCO) has been established, which disposes of the mandate to assess and reach opinions on submitted PIPs and requests for waivers and deferrals. Moreover, the obligation to develop medicinal products in and for children as well as exemptions (according to Article 9, generics, biosimilars, hybrids, well established use, herbals, homeopathics) are defined. Incentives and penalties are also laid down. EMA has published a number of related guidance, recommendation, and questions and answers documents providing detailed information on the points to consider. The Commission guideline on "the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies" (2014/C 338/01 [25]) provides useful procedural aspects to be covered when dealing with PIP. It is stressed that a request for deferral needs to be filed timely – usually before entering clinical phase II – and that it must be profoundly justified. Sometimes safety data in adults are not yet sufficient to guarantee a minimal risk in children.

In general the timely preparation of a paediatric program and establishment of internal (if available) and external experts is as much a key element as close and regular contact to the competent authority (specifically the appointed EMA coordinator and assessor) via teleconferences and scientific advice meetings before submission of the PIP or deferral request.

Figure 6 (Maciulaitis 2012) intends to summarise the stages of development of the combined ATMP including some crucial steps outlined in sections 4.1.1 and 4.1.2. It should be noted that Scientific Advice is not necessarily to be performed at exactly the stage and in the order pictured in figure 6 but at relevant milestones during development mentioned in section 4.1.2.1.

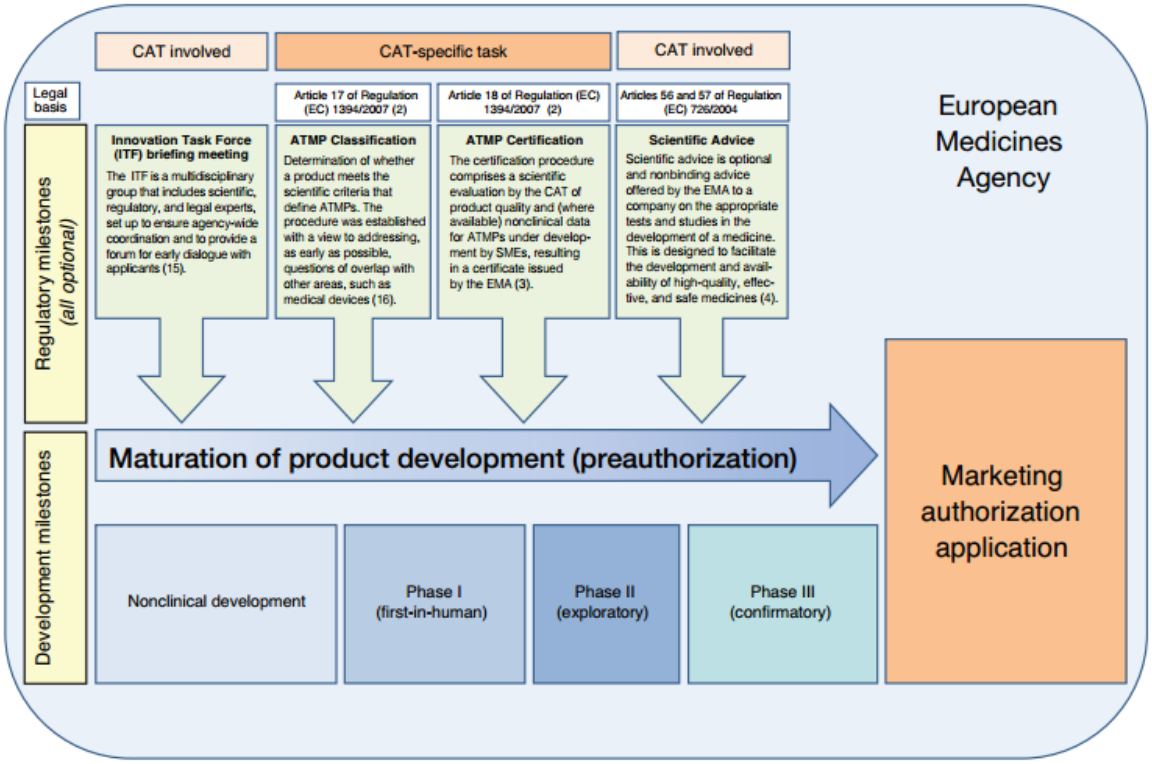

Fig. 6: Overview of development stages of the (combined) ATMP taking into account regulatory and scientific development milestones, legal basis, and involved stakeholders (Maciulaitis 2012)

4.2 Scientific and developmental steps

With knowledge of and compliance with aforementioned procedural steps the applicant can lay the foundation for crucial development stages of the combined ATMP. Non-clinical and early clinical aspects thereof will be outlined in this section and suggestions for development without any claim for comprehensiveness (given the lack of true authority advice in this scenario description) are made.

The adequate and authority-confirmed classification (reference is made to section 4.1.1.3) of the product under development has to be seen as basis for any considerations before entering non-clinical development. Once classification has been performed the corresponding specific guidelines can be applied in order to define the overall testing strategy and to characterise the product's risk-profile.

The variety of guidelines described in this thesis as well as publications showing the non-clinical testing strategy for previously authorised ATMP again make clear the need for specific product-tailored development programs.

The following considerations are based on the assumption that the combined ATMP under evaluation can be classified as a combined GTMP consisting of a non-biodegradable encapsulated cell technology device (Yasukawa 2010) and genetically modified allogeneic cells.

4.2.1 Essential aspects of characterisation of the combined ATMP

Although the overall product characterisation clearly includes quality aspects, which are principally not focused on in this thesis, they will be described here briefly because of their fundamental role for further development and during the certification process (reference is made to section 4.1.1.4).
The applicant has to define and establish a rationale for a range of essential characteristics of the combined GTMP ([13], [16]).
As for the genetically modified cells cornerstones are

- development genetics (selection markers e.g. during screening, fidelity of replication system, identity/viability/integrity of gene sequence, manipulation of gene sequence e.g. by insertion of promoters, number of gene copies, identity/suitability of vector system, manipulation of lipoplex/LPX vector e.g. through hydrophilic coating, vector integration profile/gene transfer system, purity and stability of genetic material etc.)
- production (starting materials, excipients, potential adventitious agents, origin of cells/donor/cell bank description, isolation/selection of cells, *in vitro* cell manipulation, in-process controls, batch definition etc.)
- purification processes
- product characterisation of the finished product and its individual components
- consistency (conformity of each produced batch with specified quality) and traceability
- further details are given in the guidelines cited above, section 2.1.3 and related Annex I, Part IV of Dir. 2001/83/EC

For the device part of the combined GTMP similar requirements are to be met regarding characterisation of the manufacturing process, materials and their components. For the specific encapsulated cell technology thorough descriptions of its

- scaffold's structure and features (compatibility, potential uncontrolled leakage of modified cells, potential inadvertent degradation, (long-term) stability, mechanical resistance/reinforcement structures, risk of toxicity)
- semi-permeable fiber membrane (permeability for nutrients and therapeutic proteins, non-permeability for immunological components/real-life degree of immunoprotection, definition of pore-size and molecular weight cutoff, stability, compatibility, risk of toxicity)
- risk of microbial contamination
- sterilisation process
- economical and technical features
- method of implantation
- seal components and suture clip (reliability, compatibility)

- features enabling long-term survival of genetically modified cells

need to be provided (Lathuilière 2015). Reference is also made to section 2.1.3 and related Annex I of Dir. 93/42/EEC.

4.2.2 Points to consider and suggestions for a non-clinical testing strategy with regard to technical guidelines and the risk-based approach

Scientific guidelines focusing on non-clinical development strategies for GTMP are consistent regarding the cornerstones of investigations to be carried out. These are likewise reflected by [3] and [17]. Thus studies demonstrating

- Proof of concept (primary pharmacodynamics)
- Biodistribution (pharmacokinetics)
- Toxicology

must be performed in any case. The extent of the studies covering the different categories is also determined by the product-specific risk profile that should be established as early as possible and that is derived from the planned clinical use [8].

Proof of concept (primary pharmacodynamics)

To achieve proof of concept or proof of principle, adequate and relevant nonclinical models, *in vitro* or *in vivo*, have to be established. Results from respective studies are meant to at least provide information on the product's mechanism of action and support the potential clinical effect.

In terms of monogeneic retinal diseases the majority of published data is generated through *in vivo* investigations. Usually such diseases – as well as complete achromatopsia caused by ATF6 deficiency (reference to section 3 is made) – lead to morphological and consequentially functional defects e.g. foveal hypoplasia, disruption of the cone photoreceptor layer (Kohl 2015), pathological electroretinography results and/or clinical symptoms including visual acuity impairment. Treatments aim at alleviating such symptoms and their therapeutic effects do not seem displayable in available cell lines. Therefore apart from the mechanism of action also feasibility of the therapeutic principle needs to be shown *in vivo.*

However, in case of a GTMP involving genetically modified cells meant to produce therapeutic agents, the *in vitro* demonstration of adequate protein expression and release from the fibroblast cells belongs to the therapeutic concept. Additionally the demonstration of functionality involving the device part should be endeavored by using e.g. a nutrient *in vitro* environment imitating vitreal fluid. For viability and functionality evaluations PCR and immunohistochemistry of the *in vitro* cells and proteins should be performed. Once these preliminary functionalities have been shown positively, animal experiments can be started.

Adequate animal models for different monogeneic retinal diseases have shown to be (Ezra-Elia 2014, Michalakis 2010, Jobling 2013, Hauswirth)

- knockout mice
- naturally occurring mouse models

- naturally/due to breeding occurring dog models
- naturally/due to breeding occurring sheep models

The obvious problem of implantation of the device part into small experimental animals being impossible, leaves researchers with limited, yet important, evidence deducible from small animal investigations. However, intravitreal injection of the therapeutic agent ATF6 seems reasonable in order to determine the level of therapeutic accessibility of mouse model retina for ATF6 and the potential improvement of retinal cone function. Treated (and untreated control) mice can be tested by means of electroretinography, measurement of action potentials and functional behavior tests. After sacrifice retinal neural cells can be analysed in terms of morphology and immunohistochemistry and genotyping can be carried out. Postmortem analysis plays a crucial role also regarding toxicological and biodistributional questions and questions of possible treatment failure due to toxicity, insufficient delivery of genes and/or protein expression.

After this preliminary demonstration of primary pharmacodynamics, large animal models can be used for further investigation. Gene targeting in large animals, i.e. the creation of knockout dog or sheep or transgenic animals, has not yielded satisfactory and reproducible results on a broad basis so far. Therefore a naturally occurring gene-deficiency in a large animal adequate for testing of the disease in question or a homologous animal model has to be found. It is important to unequivocally validate the genomic status of every animal before intervention, i.e. surgical implantation of the finished combined GTMP or sham surgery in control animals. After treatment functional and morphological tests such as electroretinography, optical coherence tomography (OCT) and behavioural tests (colour vision, visual acuity) can be used for evaluating therapeutic success. It is advisable to record age and gender of treated animals in order to be able to evaluate possible heterogeneity in disease manifestation. Planned juvenile studies might be worth considering with regard to a potential paediatric investigation plan (PIP) (reference is made to section 4.1.2.4). In addition, a special focus has to be laid on potential immunologic reactions influencing therapeutic efficacy and model adequacy or necessity of administration of an immunosuppressant.

Biodistribution (Pharmacokinetics)

For investigation of biodistribution of the therapeutic agent both small and large animals have to be used to enable evaluation of biodistribution after injection alone and after implantation of the GTMP in connection with the encapsulated cell technology device part. The testing of the finished product including the device part is of utmost importance because only then knowledge on the *in vivo* behavior of the cells and their products can be gained and the contribution of the delivery device to the GTMP's biodistribution and activity can be evaluated. Wild-type animals are usually used and are administered different doses of cells expressing different doses of therapeutic protein. Sacrifice of animals takes place at different time points to assess the level of clearance from plasma and the maximal amount, duration and course of decline of tissue accumulation of ATF6. Thus kinetic studies also provide valuable information as to survival and functional stability of genetically modified cells in adequate animal models ([15]).

The highest concerns might emerge from potential immunological reactions in experimental animals. Respective observations provide useful information regarding toxicological consequences.
A common and frequently demanded kinetics-related safety problem of GTMP is the risk of inadvertent germline transmission of gene transfer vectors. In non-clinical studies male and female gonads are therefore analysed with regard to possible dissemination of vector DNA. According to the corresponding guideline this risk is considered very low in products involving human genetically modified cells. Thus respective studies are not recommended [18].
Based on biodistribution study results the need for Safety pharmacology studies has to be determined. ATF6 is a ubiquitously expressed regulator of the globally occurring unfolded protein response, which could theoretically lead to adverse events in the CNS, cardiovascular or respiratory system. However, the eye as a whole and especially the subretinal region and vitreal cavity as a therapeutic target (under avoidance of intravascular or intramuscular injections) are known to be a space from where both classical immune response and more than minimal systemic dissemination of therapeutic agents are unlikely to emerge (Taney 2015).

Toxicology

When it comes to toxicity studies product-specific tailoring of the study program is again of high importance to address concerns that might only or specifically arise in connection with this medicinal product-medical device-combination product.
The selection of the most relevant animal species for evaluation of toxicity is crucial and if only one species is used route and method of administration should mimic the clinical situation, i.e. the complete finished product has to be tested. The rationales for species selection and dosing have to be justified regarding possible future doses in early clinical trials.
When determining the amount of protein release by the cell encapsulating device and its microporous semipermeable fiber membrane, e.g. by setting the number of cells and the pore size of the membrane, dose considerations are already made and fixed to a certain extent. The corresponding design of the delivery device has to be justified. To test different doses, single-dose toxicity studies under administration of the pure therapeutic protein in mice seem reasonable. With endpoints such as influences on the cardiovascular or respiratory system as well as overt signs of illness like weight loss or changed feeding behavior and microscopic as well as macroscopic tissue pathologies, it makes sense to incorporate such investigations into the primary pharmacodynamics and/or biodistribution studies. This applies to both small and large animals species.
Repeated dose toxicity studies are required in the current case because of planned clinical long-term activity of the combined GTMP within the human organism after single implantation. They should mimic clinical administration as far as possible. Aforementioned dogs or sheep might be adequate. Generally the duration of such studies should be 6 months or longer, depending on the persistence of the GTMP within the delivery device (tested in corresponding stability and/or biodistribution studies) and of the anticipated potential risks. Also in this context it might not always be necessary to perform

stand-alone studies. Endpoints should cover the requirements determined by the "Guideline on repeated-dose toxicity studies" (CPMP/SWP/1042/99 [26]). The goal of long-term observation and analysis of adequate animal species receiving the combined GTMP regarding dose, route and method of administration in analogy to the planned clinical administration is once to confirm *in vivo* what was already observed *in vitro* with regard to quality data and, additionally, to evaluate the influence on large human-like organisms. This especially applies to the used encapsulated cell technology of the delivery device, the biocompatibility of which has to be shown regarding the contained genetically modified cells and the tissue at the site of implantation. Also uncontrolled leakage and degradation of the material cannot be excluded or evaluated before application of the device in a human-like *in vivo* environment.

The medical device and its materials - to be proven biocompatible - might also provoke the necessity for genotoxicity studies, which are usually not deemed necessary in gene transfer products. The same applies to conventional carcinogenicity studies and germline alterations in GTMP and GTMP involving genetically modified cells.

A subject of higher importance is the triggering of possible immunogenicity within the meaning of a host reaction to the implanted human cells. The administration of an immunosuppressant agent to the experimental animals may be necessary in order to maintain toxicological evaluability. On the other hand, and as mentioned before on the basis of previous scientific experience the mammalian eye seems to be "an immunologically privileged space where classical immune responses are limited" due to the presence of the blood–ocular barrier (Taney 2015).

The testing of local tolerance after implantation of the delivery device regarding both the device and the contained cells is another important point to consider. But also in this case evidence may be drawn from other ongoing animal studies.

In general it can be stated that the amount of evaluation results available on the delivery device determines the study design related to concerns that have to be addressed due to its contribution to the finished product. If it has already been approved by a notified body while containing a different medicinal product (e.g. ATMP, antimicrobial or anti-inflammatory agents) complementing studies have to be performed to characterise its contribution to the activity of the GTMP. Accordingly, the exhaustiveness of studies may reach a higher level with less knowledge or no expert approval available.

This short outline (with reference to the guidance documents [12], [13] and [17]) of a possible toxicology study program aims to make clear the required product-specific elaborateness and at the same time stresses the flexibility, with which such a scientific challenge can be approached.

<u>Risk profiling of the combined GTMP</u>

As mentioned before the risk profiling of the combined GTMP (and every ATMP in general) is a process that is usually initiated during early non-clinical phase and accompanies practically all steps of development (reference is made to section 2.1.2 and guidance document [8]). Likewise guidance document [3] describes its purpose as follow: "The risk analysis is performed based on existing knowledge of the type of product and its intended use. Especially the risk analysis exercise is of critical importance as it would help

the applicant to think through the process since the very beginning and plan in advance the approaches to be taken and studies to be performed during the development of the product.”
Risks usually associated with the clinical use of ATMP according to scientific guidance, which are applicable to the combined GTMP in question, are

- unwanted immunogenicity
- tumour formation
- treatment failure
- unwanted tissue formation
- inadvertent germline transduction (unlikely)
- toxicity due to degradation/leaching of toxic compounds or lacking biocompatibility

  of the delivery device, unwanted alteration of cell homeostasis, unwanted cell/organ targeting or lacking selective targeting, deregulated therapeutic gene expression, contaminants from the production process

The risk factors contributing specifically to each identified risk have been attempted to be addressed in the suggestions for non-clinical testing strategy in this section. It is practically not possible to attribute one risk factor to one identified risk. Far more often risk factors are interlinked in their impact on more than one specific risk. Obvious examples are the different risk factors influencing the possibility of treatment failure (inappropriate cell characteristics, expression level and quality of the therapeutic protein, impurities, non-selective biodistribution, non-adequate animal models, inadequate device biocompatibility, patient-related factors etc.) or toxicity (expression level of the therapeutic protein and potential false or overexpression, non-selective biodistribution, inadequate device biocompatibility, patient-related factors etc.).
The evaluation of product-specific relevance of risk factors regarding the according identified risk enables a scientific description of the risk factor-risk relationship and is based on specific scientific knowledge gained so far or already available. As an example the risk of immunogenicity as mentioned several times can be evaluated in relationship with risk factors such as non-selective biodistribution, questionable relevance of animal models or patient-related factors. According to the knowledge already available in this matter with specific regard to the mammalian ocular space and based on possibly newly generated data within the current study setting, the profile of the identified risk ‘unwanted immunogenicity’ may be described as low to moderate.
As development progresses each product-specific risk should be accordingly profiled as a goal in order to support a marketing authorisation application.

The risk-based approach is considered largely appropriate for the non-clinical and clinical development of ATMP by regulatory authorities. In relation with the quality of an ATMP, several other risk management model approaches have been under discussion. A commonly used approach is the heuristic, pseudo-quantitative and highly structured failure mode and effect analysis/failure mode and critical effect analysis risk analysis technique (FMEA/FMCEA), which often accompanies cell therapy manufacturing. It is associated with direct estimation of severity, occurrence and detection, particularly taking into account potential human errors capable of affecting the quality of the final cell product.

FMEA/FMCEA involves charting the probability of failure modes against the severity of their consequences, thus estimating the respective failure mode's criticality level and allowing remedial effects to be directed where they will produce greatest value (Lopez 2010). Risk prioritisation and potential human errors play a prominent role in this quality-directed approach, whereas the risk-based approach for risks arising during non-clinical and clinical development are for logical reasons mainly pharmacological in nature.

4.2.3 Points to consider and suggestions for early clinical investigation for the development of the combined GTMP

In this section suggestions for a possible first-in-human clinical investigation are meant to be made. Regulatory, legal and procedural aspects have been addressed in sections 2 and 4.1 and should be read in conjunction with this section.

When approaching clinical development phase of an ATMP or a combined GTMP designed for the treatment of a rare disease it is obvious, that the conventional clinical study program involving healthy volunteers for purely pharmacological and toxicological questions followed by randomised trials including treated patients and untreated placebo groups is not feasible for ethical as well as practical reasons. In addition, it is unlikely to impossible to reach large study sizes usually common in patient populations suffering from much more frequent diseases. Patient groups in early trials might not even reach double-digit numbers. Moreover, the dose used in first-in-human trials is not always well deducible from large animal nonclinical studies. The reasons for this are the species-specific biological *in vivo* environment and the individual species- and patient-related factors, which play a crucial role in the pharmacological, therapeutic and toxicological effects of the finished product. Therefore a thorough understanding of the GTMP's mechanism of action and the role of the delivery device are essential for the performance of an elaborately planned and meticulously thought out clinical trial phase.

The decision on the first human dose should be based on the rationale for the use of the combined GTMP in human subjects (justification that the therapeutic agent produced by the genetically modified cells is assumed to modify the disease pathway), on biological effects observed in animals with appropriate study designs that confirm the assumptions underlying the rationale, and on the results of toxicity studies, which mainly refine dose recommendations [17].

The first clinical trial in a limited number of patients well characterised regarding their geno- and phenotype should be designed for determining whether the effects observed during previous developmental steps are attributable to the transfected gene (proof of concept in humans). In the present case direct pharmacodynamics and pharmacokinetics evaluation is not possible and has to be correlated with and assessed by means of appropriate functional parameters. Otherwise the level of therapeutic protein expression and the level of efficacy at the organism's target cells are hard to be judged. Meaningful endpoints have to be chosen and might e.g. be outcomes of testing best-corrected visual acuity, visual and spectral field sensitivity, visual field, adaptation to dark and light, electroretinography, optical coherence tomography (OCT) and laser ophthalmoscopy for

achieving high-resolution images of cone photoreceptors. The procedure of implantation of the delivery device containing the genetically modified cells must meet the essential requirements described in section 2.1.3 in terms of handling, experience and expertise. Since no placebo group can be established it is recommendable to perform treatment surgery in one eye and sham surgery in the other (control) eye of the participant. For logical reasons the respective eye's assignment should happen on a randomised basis (Talcott 2011).

Based on experience from animal studies the concomitant administration of immunosuppressive agents needs to be considered to avoid harmful host-versus-graft reactions.

Duration of monitoring and follow up, also at this early clinical stage, should be appropriately chosen in view of the long-term character of the treatment and might not fall below 24 months or longer. Also when conclusions from functional outcome might already have been drawn and advanced phase clinical trials with adapted dosing etc. are being planned, patients need to be continuously followed up according to product- and disease-specific conditions and to respective scientific guidelines [10]. Prolonged follow-up is not only meant to cover both immediate and late-onset adverse events but also to keep levels of persistence and functionality of the cells and delivery device under surveillance. Short and long-term side effects need to be managed my means of a sufficient pharmacovigilance system, which allows initiation of adequate reactions to adverse events (e.g. in case of need of implant removal or concomitant medication administration) as well as continuous evaluation of the combined GTMP's risk profile.

5 Conclusion

In this thesis the regulatory and scientific landscape for nonclinical and early clinical development of an ATMP, specifically a combined GTMP consisting of genetically modified allogeneic cells encapsulated in a special non-biodegradable medical device technology for ocular implantation and sustained release of a therapeutic agent, clinically relevant for a rare form of inherited achromatopsia, was outlined.

Regulatory and legal provisions such as relevant regulations, directives and guidance documents released by the respective stakeholders have - although of non-binding character - shown to offer a framework for this highly challenging project at most.

Unlike chemical synthetic medicinal products, steps in development of GTMP, same as of other biopharmaceuticals, have far more to be taken in a flexible, product-specific, and intelligent manner, in order to create a thought out and successful development plan. Depending on the type of product (influencing its manufacturing steps, applicability in animal models, dose-finding and surveillance in humans etc.) a tailored and adequate study program needs to be defined. On the one hand, this necessity provides the opportunity to combine studies - nonclinical and clinical - in a flexible way, in order to avoid pointless investigations and spare valuable resources on the way towards an adequate dataset ready for marketing authorisation. On the other hand, compelled non-conventional study programs, are at even greater risk of failure because possibilities for the demonstration of certain facts and/or effects may be limited, e.g. there may not exist an appropriate animal

model or *in vitro* method for every point to be proved and first human application may have to be based on a less robust body of evidence than in case of synthetic medicinal products. The development of a treatment for a rare, yet debilitating disease like achromatopsia might therefore be hindered and prolonged by a range of obstacles difficult to foresee. A comprehensive risk analysis at an early stage is one crucial measure to mitigate the impact of various pitfalls.

As stressed several times, regular communication with the competent authority, especially with the respective project coordinator as focal point for further contacts e.g. with other expert groups like notified bodies, ethics committee members etc., at key timepoints is essential to be considered and to stick to. Meaningful and constructive liaison with regulatory and scientific stakeholders might prevent the applicant from performing investigations that are superfluous or not success-oriented. Liaison possibilities are diverse, especially for SME, and should be exploited in a reasonable manner.

Therefore this thesis can only point out important cornerstones of a possible fictional development scenario without claiming to present a comprehensive investigation plan. This applies to both regulatory and above all scientific issues. In the current context suggestions for development and optional regulatory measures were made. During development there might, however, emerge conditions imposing strategic amendments.

For these reasons an appropriate approach has to be taken and followed ultimately in accordance with current regulatory provisions and in coordination with experts from the competent authority. A multi-disciplinary and transparent environment is the key component for efficient and successful development of a combined ATMP.

6 Annex

6.1 List of references

Guidance documents

[1] Procedural advice on the provision of scientific recommendation on classification of advanced therapy medicinal products in accordance with article 17 of regulation (EC) no 1394/2007 (EMA/CAT/99623/2009 Rev.1)

[2] Reflection paper on classification of advanced therapy medicinal products (EMA/CAT/600280/2010 rev.1)

[3] Guideline on the minimum quality and non-clinical data for certification of advanced therapy medicinal products (EMA/CAT/486831/2008/corr)

[4] Procedural advice on the certification of quality and nonclinical data for small and medium sized enterprises developing advanced therapy medicinal products (EMA/CAT/418458/2008/corr.)

[5] CAT's Rules of Procedure (EMA/CAT/454446/2008 rev. 1)

[6] Mandate, Objectives and Rules of Procedure for the EMA/CAT and Medical Devices' Notified Body (EMA/CATNB) Collaboration Group (CG) (EMA/327938/2010)

[7] Procedural advice on the evaluation of combined advanced therapy medicinal products and the consultation of Notified Bodies in accordance with Article 9 of Regulation (EC) No. 1394/2007 (EMA/354785/2010)

[8] 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)

[9] Detailed guidelines on good clinical practice specific to advanced therapy medicinal products (ENTR/F/2/SF/dn D(2009) 35810)

[10] Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products (EMEA/149995/2008)

[11] Questions and Answers on Gene therapy (EMA/CHMP/GTWP/212377/2008)

[12] Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products (Draft) (EMA/CAT/80183/2014)

[13] Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells (EMA/CAT/GTWP/671639/2008)

[14] Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)

[15] Guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006)

[16] Note for guidance on the quality, pre-clinical and clinical aspects of gene transfer medicinal products (CPMP/BWP/3088/99)
[17] Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/ CHMP/GTWP/125459/2006)

[18] Guideline of non-clinical testing for inadvertent germline transmission of gene transfer vectors (EMEA/273974/2005)

[19] Reflection paper on design modifications of gene therapy medicinal products during development (EMA/CAT/GTWP/44236/2009)

[20] User guide 'Addressing the needs of small and medium sized enterprises'

[21] European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance (EMA/691788/2010 Rev. 7)

[22] Detailed procedural guidance (EMA/710915/2009 Rev. 13)

[23] Relevant sources for orphan disease prevalence data (EMA/452415/2012 Rev. 1)

[24] Guideline on the need for nonclinical testing in juvenile animals of pharmaceuticals for paediatric indications (EMEA/CHMP/SWP/169215/2005)

[25] Commission guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01)

[26] Guideline on repeated-dose toxicity studies (CPMP/SWP/1042/99)

Further documents

ISO-10993 (Biological Evaluation of Medical Devices Part 1: Evaluation and Testing within a risk management process)

ISO 13485 (Medical devices - Quality management system – Requirements for regulatory purposes)

ISO 14937 (Sterilization of healthcare products)

ISO 14155 (Clinical investigation of medical devices for human subjects – Good clinical practice)

Outcome of SME office survey on the implementation of the SME regulation – Commission Regulation (EC) No 2049/2005 (EMA/733642/2011)

Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (COM(2014) 188 final)

Commission Recommendation 2004/361/EC of 6 May 2003 concerning the definition of micro, small and medium-sized enterprises (notified under document number C(2003) 1422)

<u>EU Legislation – Regulations and Directives</u>

- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Consolidated version: 05/06/2013)

- 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 (Consolidated version: 02/07/2012)

- Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (Consolidated version: 07/08/2009)

- Commission Regulation (EC) No 847/2000 of 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and‘clinical superiority’

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Table of Figures

6.2 Abbreviations and acronyms

AMG	Arzneimittelgesetz
ATMP	Advanced therapy medicinal product
CAT	Committee for Advanced Therapies
CBMP	Cell-based medicinal products
CEN	Comité Européen de Normalisation
CENELEC	Comité Européen de Normalisation Électrotechnique
CG	Collaboration Group
CHMP	Committee for Medicinal Products for Human Use
COMP	Committee for Orphan Medicinal Products
CPMP	Committee of Proprietary Medicinal Products
CRO	Clinical research organisation
CTA	Clinical trial authorization
CTD	Common Technical Document
Dir.	Directive
DNA	Deoxyribonucleic acid
EC	European Commission
EEA	European Economic Area
EEC	European Economic Community
EMA	European Medicines Agency
EMA/CAT-NB	EMA/CAT and Medical Devices' Notified Body
ERG	Electroretinography
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FDA	Food and Drug Administration
Fig.	Figure
FMEA/FMCEA	Failure mode and effect analysis/failure mode and critical effect analysis
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
GTMP	Gene therapy medicinal product
GTWP	Gene Therapy Working Party
HTA	Health Technology Assessment
IB	Investigator's brochure
IMPD	Investigational medicinal product dossier
ISO	International Organization for Standardization
ITF	Innovation Task Force
LoQ	List of questions
MAA	Marketing authorisation application
MD	Medical device
MedDRA	Medical Dictionary for Regulatory Activities
NB	Notified body

OTC	Optical coherence tomography
PIP	Paediatric Investigation Plan
Reg.	Regulation
Rev.	Revision
rev.	revised
SA	Scientific Advice
SAWP	Scientific Advice Working Party
sCTMP	Somatic cell therapy medicinal product
SME	Small and medium-sized enterprise
SOP	Standard operating procedure
SWP	Safety Working Party
TEP	Tissue engineering product

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

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Unterschrift