The Hospital Exemption, a regulatory option for unauthorised advanced therapy medicinal products

Wissenschaftliche Prüfungsarbeit

zur Erlangung des Titels

„Master of Drug Regulatory Affairs“

der Mathematisch-Naturwissenschaftlichen Fakultät
der Rheinischen Friedrich-Wilhelms-Universität Bonn

vorgelegt von
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aus Berlin

Bonn 2014

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LIST OF ABBREVIATIONS

ACI	Autologous chondrocytes implantation
ACI-M	Matrix-associated autologous chondrocytes implantation
AEMPS	Agencia Española de Medicamentos y Productos Sanitarios / Spanish Medicins Agency
AMG	Arzneimittelgesetz / German Medicinal Products Act
AMHV	Arzneimittel-Härtefall- Verordnung / Ordinance on Medicinal Products for Compassionate Use
AMNOG	Gesetz zur Neuordnung des Arzneimittelmarktes / The Act on the Reform of the Market for Medicinal Products
AMWHV	Arzneimittel- und Wirkstoffherstellungsverordnung / Ordinance on the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients
ATMP	Advanced Therapy Medicinal Product
BE	Belgium
BMG	Bundesministerium für Gesundheit / German Federal Ministry of Health
cATMP	Combined ATMP
CAT	The Committee for Advanced Therapies
CT	Clinical Trial
CTD	Common Technical Document
CU	Compassionate Use
DE	Deutschland / Germany
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information / The German Institute of Medical Documentation and Information
Dir.	Directive
DK	Denmark
EC	European Community
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
Fimea	Finish Medicines Agency
G-BA	Gemeinsamer Bundesausschuss / The Federal Joint Committee
GBM	Glioblastoma multiforme
GCP	Good Clinical Practice
G-DRG	German Diagnosis Related Groups System

GKV	Gesetzliche Krankenversicherung / Statutory Health Insurance
GMP	Good Manufacturing Practice
GTMP	Gene Therapy Medicinal Product
HE	Hospital Exemption
HPRA	Health Products Regulatory Authority
ICRS	International Cartilage Repair Society
InEK	Institut für das Entgeltsystem im Krankenhaus / The Institute for the Hospital Remuneration System
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesunheitswesen / Institute for Quality and Efficiency in Health Care
IZG	Health Care Inspectorate in the Netherlands
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MACI	Matrix applied characterised autologous cultured chondrocytes
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board
MHRA	Medicines and Healthcare Products Regulatory Agency
MS	Member State
NA	Not applicable
ND	Not determined
NCA	National Competent Authority
NL	Netherlands
No	Number
Nr.	Nummer / Number
NUB	Neue Untersuchungs- und Behandlungsmethoden / New examination and treatment methods
NW Bio	Northwest Biotherapeutics
PEI	Paul-Ehrlich-Institute
QPPV	Qualified Person for Pharmacovigilance
Reg.	Regulation
ROI	Return on Investment
sCTMP	Somatic Cell Therapy Medicinal Product
SGB V	Sozialgesetzbuch V / Book Five of the German Social Code
SME	small- and medium-sized-enterprise
SmPC	Summary of Product Characteristics
TEP	Tissue engineered Product

TFG	Transfusionsgesetz / German Transfusion Act
TPG	Transplantationsgesetz / German Transplantation Act
TPG-GewV	TPG-Gewebeverordnung / Ordinance on tissues and organs
UK	United Kingdom
US	United States of America

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1 INTRODUCTION

The advances in biomedical research in the fields of genetics, cell biology and tissue-engineering have produced a wide range of potential medicinal products developed for innovative therapeutic approaches. These highly innovative medicinal products are considered promising candidates for the combat of diseases, which currently no or no satisfactory therapies are available against, such as Cancer, genetic disorders and neurodegenerative diseases. In particular, tissue engineered products aimed at repairment, replacement and reconstruction of tissues such as skin and blood vessels is a growing sector. Until the Regulation (EC) No 1394/2007 (1) (hereinafter referred to as "ATMP regulation") came into force on 30.12.2007 and started to apply on 30.12.2008, the regulatory framework in the European Union (EU) for these kind of products, given the term advanced therapy medicinal products (ATMPs), was very heterogeneous (2). Especially for tissue engineered products, the situation was complex as they were either regulated as medicinal products or medical devices depending on the view of the respective national competent authority (NCA) (3) (4).

The main aims of the ATMP regulation were to harmonise the market in the EU for ATMPs, protect public health and to foster innovative research and biotechnological development in Europe (5). One way to harmonise the so far divergent market for ATMPs in the EU, was to make the central marketing authorisation (MA) mandatory for all ATMPs. At the time the ATMP regulation applied, there were products already on the EU market that then classified as ATMPs according to the newly introduced definition of Tissue engineered products (TEPs) and combined ATMPs (cATMP). These products had so far been distributed under national provisions (e.g. manufacturing authorisation) in the EU Member States (MSs). A transitional period of 3 or 4 years[1] for those ATMPs was granted in Article 29 of the ATMP regulation to comply with the ATMP regulation. However, a central MA is highly demanding on costs, time and regulatory expertise. As the development of ATMPs is largely driven by academics, hospitals and small- and medium-sized-enterprises (SMEs) (6), it appears very ambitious that those companies and institutions currently developing ATMPs or having developed products that now fall under the provisions of the ATMP regulation are able to meet the demands of a central MA. The EU report on the ATMP regulation published earlier this year (7), clearly showed that only very few ATMPs managed the way through to a central MA. Another point to consider is whether a central MA is in all cases the suitable regulatory option for these companies and institutions with regards to the purpose and marketing of the products.

Importantly, an exemption from the central MA is provided for in Article 28 (2) of the ATMP regulation referring to Article 3 Nr. 7 of Directive 2001/83/EC (8). This so-called Hospital Exemption (HE) is applicable to ATMPs that fulfill a number of criteria. With the details of the HE

[1] The transitional period for Gene Therapy Medicinal Products and Somatic Cell Therapy Medicinal Products to comply with the ATMP regulation ended on 30 December 2011; the transitional period for Tissue engineered products to comply with the ATMP regulation ended on 30 December 2012.

contained in the Directive 2001/83/EC and not in the ATMP regulation itself, it has been the obligation of each Member State (MS) to implement the provisions of the HE into their national legislation. In Germany, the national requirements for the HE are provided for in Section 4b "Special provisions governing advanced therapy medicinal products" of the German Medicinal Products Act (*Arzneimittelgesetz - AMG*) (9). Hence, the term "4b autorisation" is sometimes used to refer to the HE for ATMPs in Germany.

In this master thesis, the legal provisions and national interpretation of the HE are described in detail. Although the main focus is on Germany, which is one of the leading markets for ATMPs, also other european MSs are considered. Another point of this master thesis was to investigate how the HE has been used as a regulatory option since the ATMP regulation applied from 30.12.2008, again with special focus on the latest developments in Germany. Eventually the HE is compared to other early access options for patients to unlicensed ATMPs, including Compassionate Use (CU) programmes, Clinical Trials (CTs) and Named Patient Use. However, details on the early access to market options in the context of the central MA, such as conditional approval, approval under exceptional circumstances or orphan drug approvals are not presented in this master thesis. Eventually, the HE is discussed whether it represents a (permanent and/or transitional) regulatory option for unauthorised ATMPs and whether this exemption is misused to circumvent the central MA.

2 LEGAL FRAMEWORK FOR ATMPS IN THE EU

The current legal framework for ATMPs in the EU consists of Regulation (EU) No 1394/2007 (1) in conjunction with other applicable (pharmaceutical) laws. To be more concise, the ATMP regulation was developed as a *lex specialis* of Directive 2001/83/EC (8) to provide the regulatory framework specific for ATMPs in terms of authorisation, supervision and pharmacovigilance (see Article 1 of the ATMP regulation). The centralised procedure to obtain a MA, as described in Regulation (EC) No 726/2004 (10), became obligatory for ATMPs (see Article 27 Nr. 3 of the ATMP regulation). Therefore, the ATMP regulation amended both Directive 2001/83/EC and Regulation (EC) No 726/2004 with respect to the specific rules for ATMPs.

There are four types of ATMPs defined in Article 2 (1 a-d) of the ATMP regulation and Annex I part IV of Directive 2001/83/EC:

- Gene Therapy Medicinal Product (GTMP)
- Somatic Cell Therapy Medicinal Product (sCTMP)
- Tissue Engineered Product (TEP)
- Combined ATMPs (cATMP), consisting of a medicinal product and as an integral part a medical device.

While the definitions of GTMP and sCTMP were already introduced in 2003 into Annex I of Directive 2001/83/EC by the amending Commission Directive 2003/63/EC (11), TEPs and cATMP were newly defined by the ATMP regulation. For the full legal texts on the definitions see Annex II.

Specifics of ATMPs into other legal texts were implemented through the comitology procedure and guidelines by the European Commission. Details on the evaluation and certification of quality and non-clinical data for SMEs were implemented by Commission Regulation (EC) No 668/2009 (12). The scientific and technical requirements specific to ATMPs concerning quality, safety and efficacy were introduced by the Commission Directive 2009/120/EC to amend Annex I of Directive 2001/83/EC (13). The Annex 2 of the EU guidelines for Good Manufacturing Practice (GMP) was updated by the European Commission with respect to the specific requirements of ATMPs to comply with Article 5 of the ATMP regulation (14) and a guideline on good clinical practice to ATMPs was developed (15). In addition, a number of scientific and procedural guidelines and guidance documents for ATMPs have been developed by the European Medicines Agency (EMA) (16) (17).

In case ATMPs consist of human cells or tissues, Directive 2004/23/EC applies with respect to donation, procurement and testing of human tissues and cells (see Article 3 of the ATMP regulation) (18). With respect to traceability also the provisions of Directive 2002/98/EC for the collection, testing, processing, storage and distribution of human blood and blood components have to be followed (19). In case of an ATMP containing “as an integral part” a medical device, the medical

device legislation namely Directive 93/42/EEC and Directive 90/385/EEC apply (20) (21). The core legal texts applicable to ATMPs in the EU are shown in Figure 1. As shown in Figure 2, the other european legal provisions for medicinal products now also apply to ATMPs including the Paediatric Regulation (Regulation (EC) No 1901/2006) (22), the Clinical Trials Directive (Directive 2001/20/EC) (23), the Pharmacovigilance legislation (Directive 2010/84/EU (24) and Regulation (EU) No 1235/2010 (25)), the GMP Directive (Directive 2003/94/EC) (26), the Falsified Medicines Directive (Directive 2011/62/EU) (27), the Variation regulation (Regulation (EC) No 1234/2008 (28)) and the regulation on Orphan Medicines (Regulation (EC) No 141/2000) (29). As Directives have to be transposed into the national pharmaceutical legislation of the EU MSs, the respective national provisions have to be followed. Taking Germany as an example, the complete list of legal texts applicable for ATMPs on the EU and at the national level in Germany are listed in Table 9: The legal framework applicable to ATMPs in the EU and Germany.Table 9 in Annex I.

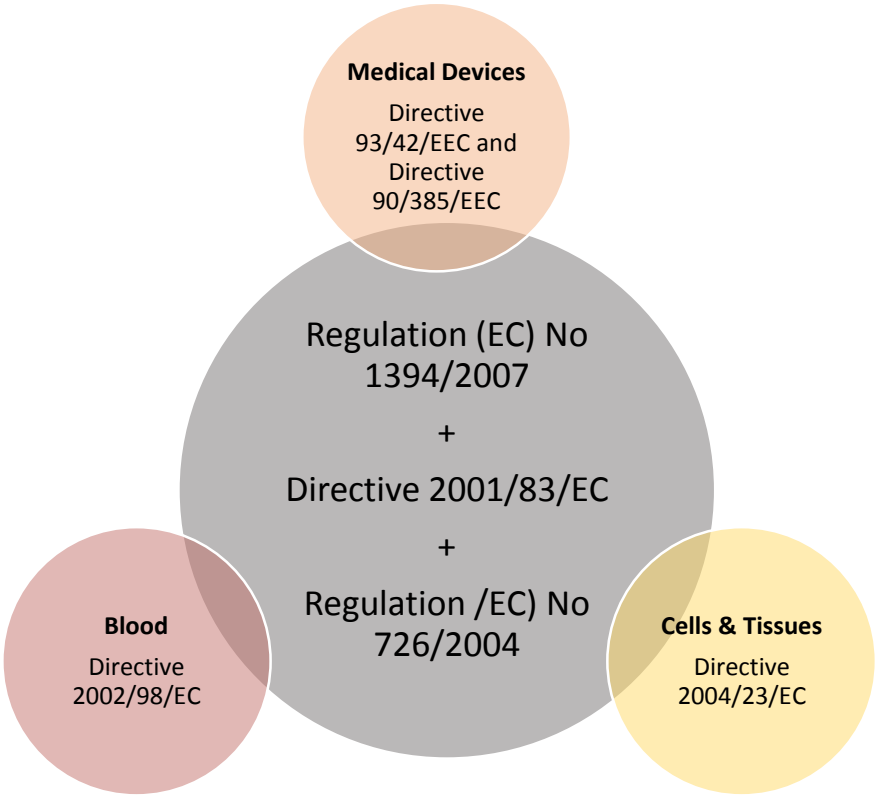


Figure 1: Core legal texts for ATMPs in the EU.

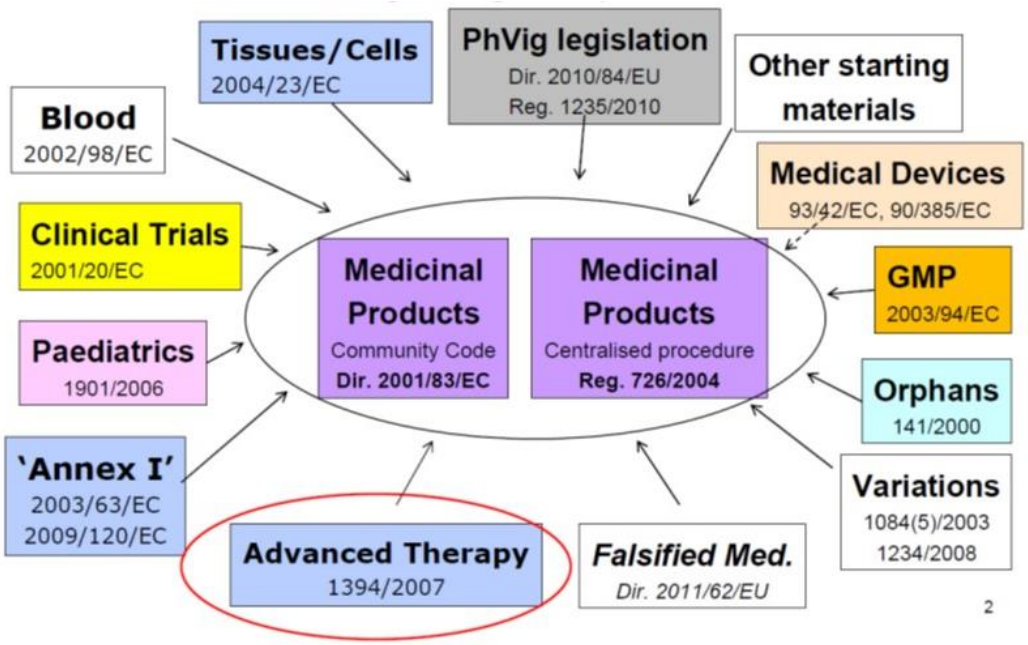


Figure 2: EU legal / regulatory framework for pharmaceuticals [modified from Salmikangas (2014) (30)].

3 THE HOSPITAL EXEMPTION (HE)

Several products which now classify as ATMPs were available on the markets of the EU MSs under national provisions, usually manufacturing licenses, before the ATMP regulation applied on 30.12.2008. According to Article 27 No. 3 of the ATMP regulation, it then became mandatory for medicinal products that classify as ATMPs to follow the centralised procedure to obtain a MA pursuant to Regulation (EC) No 726/2004 (10). The EU legal framework for pharmaceuticals (see Figure 2), which now also applies to ATMPs, sets high regulatory standards including manufacturing in compliance with GMP and the centralised procedure for obtaining a MA, which requires among others pivotal CTs and paediatric investigation plans. This puts an enormous regulatory burden on the manufacturers of ATMPs, who are mainly represented by SMEs and academic institutions with only limited regulatory expertise, budget and personnel (6). The transitional period, as defined by Article 29 (1-2) of the ATMP regulation, of 3 year for GTMPs and sCTMPs and 4 years for TEPs to obtain a central MA for existing ATMPs was relatively short. However, an exemption from the scope of Directive 2001/83/EC and thus the central MA and was introduced into Article 28 (2) of the ATMP regulation to consider certain ATMPs, which are outside the scope of the ATMP regulation. Therefore, ATMPs that were legally on the national markets on 30.12.2008 were granted a transitional period for either obtaining the central MA or to apply for the HE, if marketing was to be continued (31) (see Figure 3). Notably, the same regulatory options exist for new products as well.

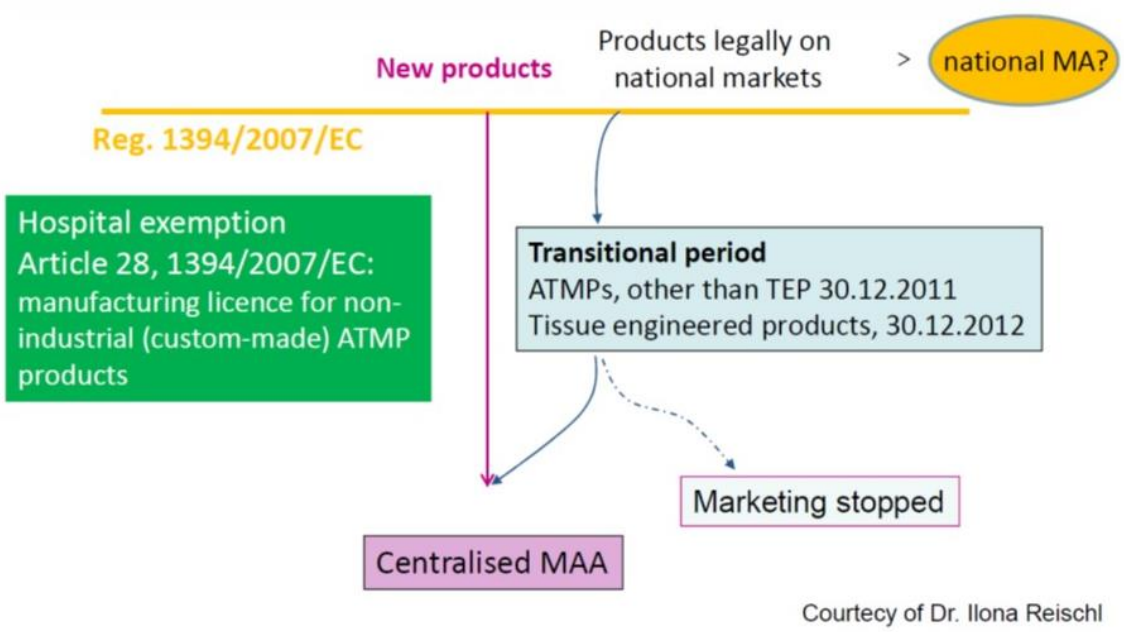


Figure 3: Regulatory options for ATMPs in the EU since coming into force of the ATMP regulation [modified from Salmikangas (2014) (32)].

Article 28 (2) of the ATMP regulation, in turn, amended Article 3 of Directive 2001/83/EC as follows:

"This Directive does not apply to:
(…)
7. Any advanced therapy medicinal product, as defined in Regulation (EC) No 1394/2007, which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.

Manufacturing of these products shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to 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." (see Article 3 No. 7 of Directive 2001/83/EC) (8).

Article 3 Nr. 7 of Directive 2001/83/EC is divided into two sub-sections. Sub-section 1 contains the cumulative prerequisites for an ATMP to be eligible for the HE:

- "prepared on a non-routine basis according to specific quality standards"
- "used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner"

- "comply with an individual medical prescription for a custom-made products for an individual patient"

Sub-section 2 contains other legal requirements for the HE with respect to manufacturing authorisation, traceability, pharmacovigilance and specific quality standards.

As stated in the preamble 6, the ATMP regulation is to provide a regulatory framework for ATMPs "(…) which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, (…)." (1). The need to exempt certain products from the highly demanding central authorisation procedure was already considered by the European Commission proposal of the ATMP regulation as of 16.11.2005 (33):

Article 28 (1):

"7. Any advanced therapy medicinal product, as defined in Regulation (EC) No […/of the European Parliament and of the Council (Regulation on Advanced Therapy Medicinal Products)*], which is both prepared in full and used in a hospital, in accordance with a medical prescription for an individual patient."

The originally proposed provisions for the HE were less detailed in terms of the legal prerequisites, and importantly, use and manufacturing of the ATMP were restricted to hospitals only. Upon controverse discussion during the legislative procedure, Article 28 was reworked and composed in a broader sense to accommodate the amendments proposed by the European Parliament (34). As a result, manufacturing of ATMPs under the HE must not take place in hopistals only. Moreover, although excluded from the scope of the ATMP regulation and Directive 2001/83/EC, the quality of the manufacturing of hospital-exempt ATMPs should be no less than those of centrally authorised ATMPs and the same pharmacovigilance and traceability requirements apply also to the exempt products.

As the european provisions for the HE are in fact contained in Directive 2001/83/EC, MSs had to implement Article 3 Nr. 7 of the Directive 2001/83/EC into their national legislation. Thus, ATMPs are exempted from the centralised MA pursuant to Article 28 (2) of the ATMP regulation according to the national provisions and their use and manufacturing are restriced to single MSs. Therefore, it is necessary to follow the legal interpretation of Article 3 Nr. 7 of Directive 2011/83/EC implemented into the national laws of the individual MSs. In case of Germany, the HE was implemented into the German AMG as Section 4b "Special provisions governing advanced therapy medicinal products" (9). As Section 4b AMG contains reference to other legal provisions, for example to Article 14 and 15 of the ATMP regulation, it is important to also fulfill the requirements of those legal texts (see section 3.1.1 Implementation of the HE in Germany).

Finally, it is important to point out that only medicinal products that classify as ATMPs according to Article 2 of the ATMP regulation are eligible for the HE and that the HE is nationally regulated according to the legal provisions of the individual MSs. As Germany is an important market for

innovative therapies including ATMPs, the following section looks in detail at how the HE has been implemented in Germany.

3.1 Implementation of the HE in Germany

3.1.1 The HE in the German Medicinal Products Act

Article 1 of the Act amending the regulations on medicinal products and other regulations as of 17 July 2009 (*Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften vom 17. Juli 2009*) (35), introduced the national provisions for the HE of Article 3 Nr. 7 of Directive 2001/83/EC into Section 4b "Special provisions governing advanced therapy medicinal products" of the German Medicinal Products Act (AMG) (35), which came into force on 23.09.2009 :

" (1) In the case of advanced therapy medicinal products which are:

1. prescribed by a doctor as an individual preparation for an individual patient,

2. prepared on a non-routine basis according to specific quality standards, and

3. used in a specialised facility for health care under the professional responsibility

of a doctor,

within the scope of the present Act, Part Four with the exception of Section 33 and Part Seven of the present Act shall not apply. The remaining provisions of the Act, as well as Article 14 (1) and Article 15 (1-6) of the Regulation (EC) No. 1394/2007 shall apply *mutatis mutandis* with the proviso that the official tasks and powers laid down therein are assumed by the competent authority or the competent higher federal authority in keeping with the tasks entrusted to them by the present Act and the holder of the authorisation pursuant to sub-section 3 sentence 1, takes the place of the marketing authorisation holder pursuant to the present Act or the marketing authorisation holder pursuant to Regulation (EC) No. 1394/2007.

(2) Prepared on a non-routine basis pursuant to sub-section 1 sentence 1 number 2 are, in particular, medicines:

1. which are manufactured in small quantities, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient, are carried out, or

2. which have not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available.

(3) Medicinal products pursuant to sub-section 1 sentence 1 may only be supplied to others if they have been authorised by the competent higher federal authority. Section 21a sub-sections 2 to 8 shall apply *mutatis mutandis*. The authorisation can be issued for a limited time. If the necessary information and documents pursuant to Section 21a sub-section 2 number 6 cannot be submitted, the applicant can submit information and documents regarding the mode of action, the anticipated effect and possible risks. The holder of the authorisation shall inform the competent higher federal authority, at specific intervals stipulated by the competent higher federal authority by means of an ordinance, about the scale of manufacture and about the data for the comprehensive assessment of the medicinal product. The authorisation shall be withdrawn if it subsequently becomes known that one of the prerequisites provided for in sub-section 1 sentence 1 had not been fulfilled; it shall be

revoked if one of the prerequisites no longer exists. Section 22 sub-section 4 shall apply *mutatis mutandis*.

(4) Enquiries about the obligation to obtain an authorisation for an advanced therapy medicinal product shall be decided by the competent authority in consultation with the competent higher federal authority. Section 21 sub-section 4 shall apply *mutatis mutandis*." (9).

Section 4b of the AMG is divided into four sub-sections. Sub-section 1 contains the prerequisites for an ATMP to be eligible for the HE. Also reference to the applicable legal framework is given and the terminology of the holder of the authorisation pursuant to sub-section 3 sentence 1 is defined as the "holder of the authorisation" to distinguish it from the term "marketing authorisation holder" (MAH) used in the ATMP regulation for centrally authorised ATMPs. Of note, the term *mutatis mutandis* implies that the provisions of the AMG within the scope indicated applies to the authorisation pursuant to Section 4b accordingly. Sub-section 2 gives explanations for the meaning of the term "non-routine production" contained in sub-section 1 Nr. 2 by listing two possible interpretations. Sub-section 3 sentence 1 contains the obligation to obtain an authorisation by the Competent Higher Federal Authority, in case the hospital-exempt ATMP is supplied to others and other legal requirements for this type of national authorisation under the HE. These entail details on the requirements for the information and documents to be submitted according to Section 21a (2-8) AMG, the obligation to obtain a manufacturing authorisation from the local competent authority, reporting intervals, expiry of the national authorisation and the legal basis for withdrawal or revocation of the national authorisation. Sub-section 4 contains the provisions how to proceed with enquiries about the obligation to obtain an authorisation for an ATMP and which competent authority takes responsibility.

According to Article 28 (2) / Article 3 Nr. 7 sub-section 1 of Directive 2001/83/EC, the prerequisites for an ATMP to be eligible for the HE concern the production and quality ("prepared on a non-routine basis according to specific quality standards"), the application ("comply with an individual medical prescription for a custom-made product for an individual patient") and the use ("used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner") of the ATMP (8). In the following section details are given on how these eligibility criteria for the HE, as outlined by the european provisions of Article 3 Nr. 7 sub-section 1 of Directive 2001/83/EC, are implemented and construed in Section 4b AMG for Germany. Table 1 gives an overview of how the european provisions of the HE criteria of Article 3 Nr. 7 of Directive 2001/83/EC compare to Section 4b AMG for Germany.

Table 1: Comparison of the legal provisions of Article 28 (2) of the ATMP regulation amending Article 3 No. 7 of Directive 2001/83/EC with Section 4b AMG regarding the legal prerequisites for ATMPs to be eligible for the HE.

Prerequisites	Art. 28 (2) Reg. (EC) No 1394/2007 / Art. 3 Nr. 7 Dir. 2001/83/EC	Section 4b AMG (Germany)
Production and quality	"(...) prepared on a non-routine basis according to specific quality standards, (...)." "(...) the specific quality standards as referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 (...)." The term specific quality standards is not further explained.	Sub-section (1) Nr. 2: "prepared on a non-routine basis according to specific quality standards, and" Sub-section (2): "Prepared on a non-routine basis pursuant to sub-section 1 sentence 1 number 2 are, in particular, medicines: 1. which are manufactured in small quantities, and in the case of which, based on a routine manufacturing procedure, variations in the procedure which are medically justified for an individual patient, are carried out, or 2. which have not yet been manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available. The term specific quality standards is not further explained.
Use	"(...) used within the same member state in a hospital under the exclusive professional responsibility of a medical practitioner, (...)."	Sub-section (1) Nr. 3: "used in a specialised facility for health care under the professional responsibility of a doctor,"
Application	"(...) an individual medical prescription for a custom-made product for an individual patient."	Sub-section (1) Nr. 1: "prescribed by a doctor as an individual preparation for an individual patient, (...)"

3.1.1.1 Legal provisions for the production and quality of hospital-exempt ATMP

According to Article 3 Nr. 7 Sub-section 1 of Directive 2001/83/EC, the ATMP eligible for the HE must be "(...) prepared on a non-routine basis according to specific quality standards, (...)" (8). In this respect the German legal implementation in Section 4b (1) Nr. 2 AMG ("prepared on a non-routine basis according to specific quality standards") is identical to the european provisions (see Table 1). In addition, the term "non-routine" is further described in Section 4b sub-section 2 AMG. Thus, an ATMP is "prepared on a non-routine basis if it is manufactured in "small quantities" and if routine manufacturing processes are amended by "variations in the procedure which are medically justified for an individual patient". However, it is not further defined what "small quantities" and "variations" actually mean. Further details on the meaning of "small quantity" are in the legal commentary on Section 4b AMG by Kügel, Müller and Hoffmann (2012) (34) and the brochure on ATMPs and their regulatory requirements and practical advice published available on the website of the innovation office of the Paul-Ehrlich-Institute (PEI), pages 12-13 (36). Both refer to the preamble of the Lower House of German Parliament (*Bundestag*) as of 16.03.2009, which states on page 43 that "small quantities" are given if the ATMP is manufactured for a small number of patients, in small amounts, whereby also a minor frequency is possible (37). According to Section 4b (2) Nr. 2 "non-routine" production is also the case if the ATMP has not yet been "manufactured in sufficient quantities so that the necessary data to enable a comprehensive assessment are not yet available". The comprehensive assessement refers to the provisions of the centralised MA pursuant to Regulation (EC) No 726/2004 (34). Importantly, the examples given in Section 4b (2) Nr. 1 and 2 AMG are not exhaustive (34). This leaves room for interpretation of non-routine manufacturing of an ATMP for cases in which none of the examples given in Section 4b (2) AMG apply. However, as the authorisation pursuant to Section 4b AMG is a special provision, the legal interpretation is considered to be rather restricted (34).

The term "specific quality standards" used in the european provisions of the HE with respect to the manufacturing of an ATMP is literally adopted into Section 4b (1) Nr. 2 AMG (see Table 1). As stated in Article 3 Nr. 7 of Directive 2001/83/EC, the specific quality standards for a hospital-exempt shall not differ from the quality requirements of a centrally authorised ATMP. However, no further details are given in Section 4b AMG with respect to the specific quality requirements for the ATMP nationally authorised pursuant to Section 4b AMG. Explanations on the term "specific quality standards" are given in the brochure on ATMPs and their regulatory requirements and practical advice on page 12 (36) and in the legal commentary Rn. 11 by Kügel, Müller and Hofmann (2012) (34). The details given there again originate from the preamble (page 43) of the Lower House of German Parliament as of 16.03.2009 (37), which states that specific quality standards apply to both, the manufacturing and the product quality of the ATMP. In particular, Section 14 (1) Nr. 6a AMG ("manufacturing and testing according to latest standards prevailing in science and technology") and the eigth chapter on safety and quality control (compliance with the German Ordinance on the

Manufacture of Medicinal Products and Active Pharmaceutical Ingredients [*Arzneimittel- und Wirkstoffherstellungsverordnung - AMWHV*] and Pharmacopoeia) of the AMG shall apply as well as the specific GMP standards for ATMPs (37). According to the legal commentary by Kügel, Müller and Hofmann (2012) Rn. 12 (34) this entails the EU-GMP guidelines and in addition the guidelines developed specifically for ATMPs by the EMA (34). Standards developed by the manufacturer of an ATMP are only acceptable in case no applicable standards have been defined for that particular case yet (37).

Of note, Article 5 of the ATMP regulation on GMP stipulates the implementations of GMP guidelines specific for ATMPs by the European Commission (1). On 31 January 2013, the revised Annex 2 of the EU guidelines for GMP for Medicinal Products for Human and Veterinary Use in Volume 4 of The Rules Governing Medicinal Products in the European Union became effective (14). The new Annex 2 takes into account the specifics for ATMPs in respect to GMP and is also applicable to hospital-exempt ATMPs.

3.1.1.2 Legal provisions for the use of hospital-exempt ATMPs

According to Article 3 Nr. 7 of Directive 2001/83/EC, the hospital-exempted ATMP must be " (...) used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, (...)." The wording in section 4b (1) Nr. 3 AMG is very similar with some minor deviations from the european provisions only (see Table 1). Instead of "hospital" the expression "specialised facility for health care" is used. Furthermore, "exclusive professional responsibility of a medical practitioner" is replaced by "professional responsibility of a doctor". According to the PEI brochure on ATMPs, their regulatory requirements and practical advise (36), which again uses the statements of the preamble of the Lower House of German Parliament as of 16.03.2009 (37), the term "specialised facility for health care" is defined in Section 14 (2) Sentence 3 of the German Law on Transfusion (*Transfusionsgesetz -TFG*) (38) as a "hospital" or other "medical institution for the treatment of patients". This comprises state and municipal hospitals as well as private clinics and also specialised medical practices (36). This means that hospital-exempt ATMPs can be used in the inpatient as well as outpatient setting in Germany. Attention should be paid to the word "specialised". In practice this means that the facilities where ATMPs under the HE are used must be specialised and thus adequately equipped (36). Furthermore, the holder of an authorisation according to the special provisions of Section 4b AMG is expected to provide for training tailored to the specifics of the ATMP (37). For example, the handling of a cell-based ATMPs requires a state-of-the-art cell culturing facility and the application of a GTMP demands specialised laboratory equipment in addition to the scientific and technical knowhow of the staff and especially the medical doctor, who administers the product.

3.1.1.3 Legal provisions for the application of hospital-exempt ATMPs

According to Article 3 Nr. 7 of Directive 2001/83/EC, the european provisions for the HE require that the ATMP must be used as "(...) an individual medical prescription for a custom-made product for an individual patient.". The German implementation in section 4b (1) Nr. 1 AMG is almost identical with only differences in wording: "prescribed by a doctor as an individual preparation for an individual patient" (see Table 1). For example, the term "individual preparation" is used instead of "custom-made product". According to the legal commentary by Kügel, Müller and Hofmann (2012) Rn. 9 (34), an "individual preparation" requires that the patient is known at the time the ATMP is manufactured and hence the ATMP represents a so-called *Rezepturarzneimittel* (34). The German term *Rezepturarzneimittel* is described in Section 7 of the Pharmacy Practice Order (*Apothekenbetriebsordnung – ApBetrO*) and refers to medicinal products without a MA that are manufactured in compounding pharmacies upon a medical prescription for an individual patient (39). Similarly, Article 3 No. 1 of Directive 2001/83/EC exempts from the obligation of a MA "Any medicinal product prepared in a pharmacy in accordance with a medical prescription for an individual patient (commonly known as the *magistral formula*)." (8). The possibility to prepare an ATMP according to Article 3 No. 1 of Directive 2001/83/EC in a pharmacy is questionable. For reasons of safety and complexity of the products, only Article 3 No. 7 of Directive 2001/83/EC should apply to ATMPs, because the HE contains requirements on the manufacturing, pharmavovigilance and traceability equivalent to centrally authorised ATMPs.

Apart of the eligibity criteria described above, Section 4b AMG contains additional legal requirements for an authorisation pursuant to Section 4b (3) AMG in case that the ATMP is supplied to others (9). It is important to point out here the two possible scenarios for the application of the special provisions of Section 4b AMG. The first scenario is that an ATMP is manufactured and applied to the patient by the same doctor in the same hospital institute. In such case and providing the eligibility criteria of Section 4b (1) are fulfilled, the ATMP falls under the HE but without the need for a national authorisation pursuant to Section 4b (3) AMG. This is because application of a medicinal product to the patient is not considered to be supply to others (40). This would be the case if an ATMP prepared from autologous cells which is manufactured and administered to the patient by the same doctor during a surgical procedure, for example. In the second possible scenario an ATMP is manufactured by another institute of the hospital or even by an external company. As an example, for autologous chondrocyte transplantation (ACI), a cartilage biopspy is taken by the doctor during a surgical procedure. Chondrocytes are then treated and expanded by an external company, which sends the chondrocyte transplant back to the hospital. The doctor then implants the chondrocyte product to the patient during a second surgical procedure. Although the ATMP is also prepared from autologous cells, the company manufacturing the chondrocyte transplant must hold an authorisation pursuant to Section 4b (3) AMG, because this company manuacturs and supplies the product to the hospital. Importantly, in both cases, a manufacturing authorisation as well as

compliance with GMP, pharmacovigilance and traceability requirements specific for ATMPs are mandatory according to Section 4b sub-section 1 AMG.

In the following section additional legal requirements of section 4b AMG are described in detail and compared to the corresponding European provisions of Article 3 Nr. 7 of the Directive 2001/83/EC.

3.1.1.4 Additional legal requirements for ATMPs under the HE

Section 4b AMG contains additional legal requirements for the authorisation, pharmacovigilance and traceability of hospital-exempt ATMPs as well as details on the evaluation and data requirements, reporting obligations and validity, withdrawal or revocation of the national authorisation pursuant to the provisions of Section 4b (3) AMG (9). A comparison to the european provisions, if applicable, is given in Table 2.

Table 2: Additional legal provisions of Section 4b AMG as compared to Article 28 (2) of the ATMP regulation / Article 3 No. 7 of Directive 2001/83/EC.

	Art. 28 (2) Reg. (EC) No1394/2007 / Art. 3 Nr. 7 Dir. 2001/83/EC	Section 4b AMG (Germany)
Authorisation	"Manufacturing of these products shall be authorised by the competent authority of the Member State."	"The remaining provisions of the Act, (…) shall apply *mutatis mutandis* with the provision that the official tasks and powers laid down therein are assumed by the competent authority or the competent higher federal authority in keepeing with the tasks entrusted to them by the present Act (...)." (Sub-section 1 sentence 2) "Medicinal products pursuant to sub-section 1 sentence 1 may only be supplied to others if they have been authorised by the competent higher federal authority." (sub-section 3 sentence 1). "Section 22 sub-section 4 shall apply *mutatis mutandis*" (sub-section 3 sentence 7)
Pharmacovigilance and Traceability	"Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004 (...)."	"The remaining provisions of the Act, as well as Article 14 (1) and Article 15 (1-6) of the Regulation (EC) No. 1392/2007 shall apply *mutatis mutandis* with the provision that the official tasks and powers laid down therein are assumed by the competent authority or the competent higher federal authority in keepeing with the tasks entrusted to them by the present Act (...)." (Sub-section 1 sentence 2)
Evaluation and data requirements	Not applicable.	"Section 21a sub-sections 2 to 8 shall apply *mutatis mutandis*. " (sub-section 3 sentence 2) "If the necessary information and documents pursuant to Section 21a sub-section 2 number 6. cannot be submitted, the application can submit information and documents regarding the mode of action, the anticipated effect and possible risks." (sub-section 3 sentence 4)

	Art. 28 (2) Reg. (EC) No1394/2007 / Art. 3 Nr. 7 Dir. 2001/83/EC	**Section 4b AMG (Germany)**
Reporting obligations	Not applicable.	"The holder of the authorisation shall inform the competent higher federal authority, at specific intervals stipulated by the competent higher federal authority by means of an ordinance, about the scale of manufacture and about the data for the comprehensive assessment of the medicinal product." (sub-section 3 sentence 5)
Validity, withdrawal or revocation	Not applicable.	"The authorisation can be issued for a limited time." (sub-section 3 sentence 3) "The authorisation shall be withdrawn if it subsequently becomes known that one of the prerequisites provided for in sub-section 1 sentence 1 had not been fulfilled; it shall be revoked if one of the prerequisites no longer exists." (sub-section 3 sentence 6)

Requirements on the authorisations of hospital-exempt ATMPs in Germany

In Germany, two type of authorisations are required for ATMPs if supplied to others under the HE, a manufacturing authorisation and a national authorisation pursuant to Section 4b (3) AMG. Section 4b sub-section 3 sentence 1 AMG states that the authorisation for placing the hospital-exempt on the market in Germany is to be issued by the competent higher federal authority (see Table 2). According to Section 77 (2) AMG it is the PEI that is the competent higher federal authority responsible for ATMPs (9). In addition a manufacturing authorisation is required (see Section 4b (3) sentence 7 AMG). The product and production specific manufacturing pursuant to Section 13 AMG is decided by the local competent authority together with the PEI according to Section 13 (4) sentence 2 AMG. In case the manufacturing of the ATMP involves the procurement and testing of tissues of human origin or of autologous blood for the manufacturing of TEPs and related laboratory testing (see Section 20b (4) AMG), a manufacturing license according to Section 20b AMG from the local competent authority is required in addition to the manufacturing license according to Section 13 AMG (41).

The innovation office at the PEI offers information, regulatory advice and coordination of scientific advice for the development of ATMPs including information on the HE pursuant to Section 4b AMG (42). The innovation office at the PEI, which was established in 2009, especially aims at supporting adademic and non-academic research groups, hospitals and SMEs in the development of ATMPs (43). Besides a decision tree for classification of medicinal products as ATMP (see Annex IV), a decision tree for Section 4b AMG is provided in English (see Annex V). More detailed information on the HE including submission, procedure, data requirements, costs, application forms and guidances as well as a FAQ document is provided on a separate website available only in German (44).

According to Section 4b AMG, the requirements on the documents and data to be submitted for an application for authorisation under HE are based on the authorisation of tissue preparations according to Section 21a, sub-sections 2-8 AMG (see full legal text in Annex III).

The forms and templates for an application pursuant to Section 4b (3) AMG are provided for by the innovation office consist of 5 parts (Modules 0, 1, 3A or 3B, 4 and 5) which are similarly structured as the Common Technical Document (CTD), which is the current standard of MA dossiers for medicinal products in the EU (45). Module 1 of the suggested application for the HE contains administrative data, Module 3A or 3B[2] consists of quality data, Module 4 is for non-clinical and Module 5 for the clinical data. Additionally, a Module 0 for the description of the medicinal product, classification as an ATMP and with regard to the fulfillment of the eligibility criteria of the HE is provided. In contrast to the standard CTD dossier, a Module 2 (Quality Overall Summary, Non-

[2] Module 3B is specific for stem cell preparations from bone marrow or peripheral blood, which are for non-homologous use

clinical Overview / Summaries and Clinical Overview / Summaries) is not suggested for the 4b authorisation application. More detailed on the required information in the individual Modules are listed in Annex VI and the current forms available from the PEI website are included on a CD attached to this master thesis. However, other application formats in CTD are acceptable such as clinical trial applications, applications forms for authorisation of tissue preparations, which can be submitted in German or English (44).

Of note, a justification that no alternative treatments or authorised medicinal products are available in Germany is expected in Module 5 of the HE applicaton dossier. This means that authorisation of an ATMP pursuant to Section 4b (3) AMG is unlikely to be successful if an alternative authorised medicinal product is available. The issue raised within the European Commisssion public consultation on ATMPs that hospital-exempt ATMPs (46) may constitute unfair competition to centrally authorised medicinal products with the same indication is therefore likely to be unsubstantiated, at least in the case of Germany.

National requirements on pharmacovigilance and traceability for hospital-exempt ATMPs in Germany

The pharmacovigialance requirements for hospital-exempt ATMPs in Germany is comparable to those for centrally authorised ATMPs according to the reference made in Section 4b (1) sentence 2 to Article 14 (1) of the ATMP regulation (see Table 2). Article 14 (1) refers to the pharmacovigilance provisions of Regulation (EC) No 726/2004 for centrally authorised medicinal products. However, instead of the EMA in case of centrally authorised ATMPs, it is the competent higher federal authority that is responsible for hospital-exempt ATMPs (Section 4b (1) sentence 2 AMG). Practically this means that for example reporting of adverse reactions to hospital-exempt ATMPs in Germany have to be directed to the PEI according to Section 63c AMG.

Of note, Article 14 (1) of the ATMP regulation contains additional obligations on ATMPs for the follow-up of efficacy and of adverse reactions. This is taken into account also for hospital-exempt ATMPs in Germany, as Module 1 of the suggested application form provided for by the PEI for the national authorisation pursuant to Section 4b (3) AMG contains a section on additional pharmacovigilance activities. Also the national pharmacovigilance obligations of the tenth chapter on Pharmacovigilance of the AMG apply to hospital-exempt ATMPs, including the nomination of a local Qualified Person for Pharmacovigilance (QPPV)[3] according to Section 63a AMG, the establishment of a pharmacovigilance and a risk management system (Section 63b AMG).

However, some controversy exist on whether the pharmacovigilance provisions of Article 24 of the Regulation (EC) No 726/2004 or the national provisions for the reporting of adverse reactions in Section 63c AMG (former Section 63b AMG) apply to hospital-exempt ATMPs in Germany.

[3] *Stufenplanbeauftragter*

According to the legal commentary of Kügel, Müller and Hofmann, (2012), the reporting obligations have to follow only Article 24 of the Regulation (EC) No 726/2004 due to the reference made in Section 4b (1) to Article 14 (1) of the ATMP regulation. In contrast to this view, Dwenger et al (41) and the commentary on the legislative process conclude that Section 63c AMG (formerly Section 63b AMG) applies (47).

Traceability, which is specifically demanded for ATMPs in Article 15 of the ATMP regulation, also applies to hospital-exempt ATMPs in Germany according to Section 4b sub-section 1 sentence 2 (see Table 2). It entails a system that ensures for each product to identify starting and raw materials from sourcing up to where the product is used (Article 15 (1) ATMP regulation) as well as a system to identify which product a patient has received (Article 15 (2) ATMP regulation). Data has to be kept for a minimum of 30 years (Article 15 (4) ATMP regulation). Importantly, these traceability systems must also comply with the provisions of the EU Tissue and Cells Directive and the EU Blood Directive (Article 15 (3) ATMP regulation). In Germany, both Directives are implemented into the German Transplantation Act (*Transplantationsgesetz - TPG*) (48) with the corresponding Ordinance on Tissues and Organs (*TPG-Gewebeverordnung – TPG-GewV*) (49) and the German Transfusion Act (*Transfusionsgesetz - TFG*) (38). Thus, traceability of hospital-exempt ATMPs containing human cells and tissues or human blood and blood components must comply also with these legal provisions.

Evaluation of hospital-exempt ATMP in Germany

The european provisions of the HE in Article 28 (2) of the ATMP regulation do not contain any details on the data requirements of hospital-exempt ATMPs for evaluation of their quality, efficacy and safety as is the case for other medicinal products including centrally authorised ATMPs (see Table 2). However, the German national provisions for the HE in Section 4b AMG refer to the same requirements as for the authorisation of tissue preparations according to Section 21a (2-8) AMG (see Section 4b sub-section 3 sentence 2). For the full text of Section 21a AMG see Annex III. Section 21a sub-sections 2-3 AMG contain details on the information and documents required for this type of authorisation. Besides administrative details (e.g. name of the applicant, name of the product) also information on the therapeutic indications, method of administration, the duration of the application as well as the functionality and risks has to be submitted (Section 21a sub-section 2 Nr. 3 and 6 AMG). As is shown in Table 2, Section 4b sub-section 3 sentence 4 AMG includes the possibility for ATMPs under the HE that limited information and documents on the functionality and the risks of the product as demanded in Section 21a (2) Nr. 6 AMG are acceptable. In this case information and documents regarding the mode of action, the anticipated effect and possible risks is sufficient. These less stringent requirements for hospital-exempt ATMPs makes it possible that even less advanced ATMPs in terms of functionality and risk evaluation have access to the regulatory option of the HE. Also, Section 21a sub-section 2 Nr. 4.-5. and 7. AMG contain requirements for the quality

data (9). These include a description of the production process, details on the products´ preservation type, shelf life and the conditions of storage, as well as the results of microbiological, chemical and physical testing and the methods used. Although the requirements according to Section 21a (2-3) AMG are far less demanding than for centrally authorised ATMPs following the provisions of Directive 2001/83/EC and Regulation (EC) No 726/2004, asssessment of safety and efficacy including a benefit/risk analysis of hospital-exempt ATMPs is performed in Germany (50). Importantly, the authorisation pursuant to Section 4b (3) AMG may be refused if the risks are found to outweigh the risks (Section 21a sub-section 6 Nr. 3 AMG).

Section 21a sub-sections 4-7 AMG contain details on procedural aspects of the authorisation pursuant to Section 4 (3) AMG. The time of the evaluation of an application for a 4b authorisation takes five months with the opportunity for clock-stops of no predefined length (Section 21a sub-section 4 AMG). The HE is officially granted by issuing an approval letter and an authorisation number (Section 21a sub-section 5 AMG). The approval may contain conditions based on Section 28 AMG. Also, the information of the public about hospital-exempt ATMPs is ensured due to reference made to Section 34 AMG, despite initially excluded from the legal framework applicable to ATMPs under the HE (see Section 4b (1) sentence 1 AMG). This not only entails publications in the German Federal Gazette on the status of the authorization such as approvals or withdrawals, but als information made available online on PharmNet.Bund to the general public such as package leaflet and Expert Information/Summary of Product characteristics (Section 34 sub-section 1a Nr. 1-4 AMG). The options to refuse the granting of a 4b authorisation are listed in Section 21a sub-section 6 AMG (9).

Reporting obligations for hospital-exempt ATMPs in Germany

As is shown in Table 2, the national provisions of the HE in Germany contain the obligation to report to the PEI "(…) about the scale of manufacture and about the data for the comprehensive assessment of the medicinal product." (Section 4b sub-section 3 sentence 5 AMG) (9). The frequency of the reporting is specifiied by the PEI. It appears that the main intention is to reassess whether the eligibility criteria of the HE are still being fulfilled and whether the data generated is sufficient to transition towards a central MA.

Validity, withdrawal and revocation of the HE in Germany

The validity, withdrawal and revocation of the HE is purely nationally regulated as there are no details given on this issue in Article 28 (2) of the ATMP regulation (see Table 2). According to Section 4b sub-section 3 sentence 3 AMG, the validity of a 4b authorisation can be restriced in time (9). Withdrawal and revocation of a 4b authorisation is possible if the prerequisistes listed in Section 4b (1) Nr. 1-3 AMG had not been fulfilled or are no longer fulfilled, respectively (see Section 4b sub-section 3 sentence 6 AMG). Also, a temporary suspension of the authorisation is possible according to Section 21a sub-section 8 AMG.

3.1.2 ATMPs currently available under the HE in Germany

Information of ATMPs holding a central MA or which are nationally authorised pursuant to Section 4b (3) AMG in Germany is available on the website of the PEI (51). Table 3 gives an overview of the name of the ATMP, the type of ATMP, the indication, date of authorisation, information on the MAH and holder of the authorisation, respectively, SME status according to the EMA registry (52) and prior market access. Currently, four ATMPs hold a central MA and seven ATMPs are nationally authorised under the HE pursuant to 4b (3) AMG. Moreover, seven out of the eleven ATMPs currently registered in Germany are TEPs. There are only two sCTMPs, of which Provenge holds a central MA, while DCVax-L is available under the HE in Germany. The only GTMP currently on the market in Germany is Glybera, which is centrally authorised.

According to Maciulaitis *et al.* (6), ATMPs are mainly clinically developed by non-commercial sponsors including academia and charitable organisations, as well as SME and "non-large" pharmaceutical companies. When registering at the EMA as an SME, it is possible to obtain several incentives such as reduced costs for scientific advice and the possibility to make use of the certification procedure. All companies that have successfully applied for a SME status at the EMA, are listed in the EMA SME registry (52). According to this registry as of November 2014, four out of the seven holders of a 4b authorisation in Germany are registered SMEs, with only Northwest Biotherapeutics GmbH (NW Bio) belonging to an international company with its headquarter based in the US, while the others are local companies based in Germany (co.don AG, UroTiss GmbH, t2cure GmbH, BioTissue Technologics GmbH, Deutsches Rotes Kreuz Blutspendedienst Baden-Württemberg - Hessen gGmbH, TETEC AG) (see Table 3). In contrast, none of the currently centrally authorised ATMPs belong to a local, Germany-based pharmaceutical company, hospital or academic institution, althoughalso uniQuere biopharma B.V. and TiGenix NV, the MAHs of Glybera and ChondroCelect, respectively, hold SME statuts according to the EMA registry. According to this overview, it becomes clear that mainly German companies make use of the possibility to apply for the HE. Still, the majority of companies that currently market ATMPs hold SME status or are non-large companies, regardless whether the ATMPs are centrally authorised or nationally authorised under the HE in Germany.

The first ATMP authorised pursuant to Section 4b (3) AMG is co.don chondrosphere by the co.don AG, which received the national authorisation pursuant to Section 4b (3) AMG on 12.12.2013 (see Table 3). In the meantime, one more 4b authorisation was issued in 2013 and five more in 2014 (see Table 3). Of note, the transitional provisions of Section 144 (2-3) AMG required that an application pursuant to Section 4b (3) AMG was submitted for ATMPs that were already on the maket on 23 July 2009 to continue to stay on the German market until the decision on the HE application was concluded (9). The deadlines to apply for the HE in Germany was the 01.08.2010 for GTMPs and sCTMPs (Section 144 (2) AMG) and the 01.01.2011 for TEPs (Section 144 (3) AMG) (9). This means that the PEI has probably received several applications for ATMPs to be authorised under the

HE. According to Buchholz, Sanzenbacher and Schüle[4] (2012) the transitional period for the HE in Germany was especially relevant for TEPs, but no application was filed for a GTMP (53).

In the published survey of the Pharmaceutical Committee in 2012 (42), it was reported that 17 ATMPs, which were legally on the German market at that time, were considered for the HE. However, at the time of the survey (during 2011), no ATMP had been authorised under the HE in Germany according to the information given in the PEI registry. Therefore, it could be assumed that evaluation of the HE for at least 17 products already on the German market had been ongoing in Germany at the time of the survey in addition to new products that had not already been marketed on 23 July 2009. From the information available on the company´s websites (54) (55) (56) and according to Sanzenbacher (2010) (57), I have confirmed that three ATMPs (co.don chondrosphere, BioSeed-C Autologes 3D-Chondrozytentransplantat and NOVOCART 3D) that have obtained a national authorisation pursuant to Section 4b (3) AMG were already on the German market on 23 July 2009 (see Table 3). For the hospital-exempt ATMPs MucoCell (58) and t2c001 (59) previous clinical experience is reported on the company´s websites . Other ATMPs that were on the German market before the application of the ATMP regulation on 30.12.2008 either proceeded to the application for a central MA (Hyalograft C), have disappeared from the market of medicinal products (e.g. CartiGro, CaReS) or are still under evaluation for authorisation under the HE. Based on Section 21a (5) sentence 3 AMG in conjunction with Section 34 (1b) sentence 2 AMG it should in principle be possible upon request to receive information about the submission of 4b authorisations from the PEI. In addition of the approval, also the withdrawal or refusal of an application for an authorisation pursuant to Section 4b (3) AMG should be made available to the public (see Section 21a (5) sentence 3 in conjunction with Section 34 (1b) AMG) in the Official Section of the Federal Gazette (60).

[4] The authors are of the Division of Medical Biotechnology of the Paul-Ehrlich-Institute (the NCA responsible for ATMPs).

Table 3: Registered ATMPs available in Germany according to the website of the PEI (as of 11.12.2014) (51).

Name of the ATMP	Type of ATMP	Therapeutic Indication	Date of authorisation	MAH / Holder of the authorisation	SME Status*	Prior Market access
CENTRAL MARKETING AUTHORISATION						
Glybera	GTMP	Glybera is indicted for adults patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and who have severe or multiple attacks of pancreatitis despite dietary fat restrictions.	25.10.2012	uniQure biopharma B.V. (NL)	Yes	No
Provenge	sCTMP	Asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.	06.09.2013	Dendreon UK Limited (UK)	Not registered	No
ChondroCelect (Charakterisierte vitale ex vivo expandierte autologe Knorpelzellen)	TEP	Repair of single symptomatic cartilage defects of the femoral condyle of the knee (International Cartilage Repair Society [ICRS] grade III or IV) in adults. Controlled trials evalutated the efficy of ChondroCelect in patients with lesions between 1-5 cm^2.	05.10.2009	TiGenix NV (BE)	Yes	No
MACI	TEP	Repair of symptomatic full-thickness cartilage defects of the knee (grade III and IV according to Outerbridge) of 3-20 cm^2 in skeletally mature adult patients.	27.06.2013	Aastrom Biosciences DK ApS (DK) [originally Genzyme Europe B.V. (NL)]	Not registered	Yes
NATIONAL AUTHORISATION PURSUANT TO SECTION 4b (3) AMG						
DCVax-L 1,25 x 106 lebende dendritische Zellen/Kryoröhrchen	sCTMP	Adjuvant therapy of Glioma (all glioma brain cancers, both Glioblastoma multiforme, the most severe grade, and lower grade, less malignant gliomas) in adult patients (newly diagnosed or recurrent) after surgical resection of the tumour and concurrent standard therapy (chemo-/ radiotherapy).	21.02.2014	Northwest Biotherapeutics GmbH	Not registered	No
co.don chondrosphere, 10-70 Sphäroide/cm2, matrixassoziierte	TEP	Acute and chronic symptomatic cartilage defects up to 10 cm2 in adults and adolescents after epiphyseal plate closure (Grade II-IV ICRS).	12.12.2013	co.don AG, Teltow (DE)	Yes	Yes

Name of the ATMP	Type of ATMP	Therapeutic Indication	Date of authorisation	MAH / Holder of the authorisation	SME Status*	Prior Market access
Zellen zur Implantation						
MucoCell	TEP	Cultivated grafts made from autologous oral mucosa cells for the treatment and surgery of a urethral stricture (male ≥18 years) if other methods failed.	23.12.2013	UroTiss GmbH, Dresden (DE)	Yes	ND
t2c001, autologous bone marrow-derived progenitor cells	TEP	Cardiovascular regenerations of tissues for cardiovascular and peripheral vascular disease - acute myocardial infarction (under specifically defined conditions) - critical limb ischaemia at category 4-5 by Rutherford.	31.03.2014	t2cure GmbH, Frankfurt (DE)	Yes	ND
BioSeed-C Autologes 3D-Chondrozytentranspl antat, 28,8 Mio. Zellen pro Einheit	TEP	Traumatic and focal cartilage defects (Grade II – IV Outerbridge; < 10 cm^2) of the knee in adults. Efficacy only assessed by clinical observational studies.	04.06.2014	BioTissue Technologies GmbH (DE)	Yes	Yes
"Zytokin-aktivierte Killerzellen (CIK-Zellen), allogen, ≤ 1x108 CD3+CD56-T-Zellen/kg Körpergewicht in ≤ 100 ml Infusionsdispersion"	TEP	Cytokine-induced killer cells (CIK-cells) for the treatment of patients with molecular recurrent leukemia after allogenic stem cell transplantation.	13.06.2014	Deutsches Rotes Kreuz Blutspendedienst Baden-Württemberg - Hessen gGmbH	Not registered	No
NOVOCART 3D	TEP	Collagen matrix-assisted autologous chondrocyte transplantation (ACI-M) for the treatment of localised profound defect of the cartilge of the knee.	29.08.2014	TETEC AG (DE)	Not registered	Yes

* SME status: registered SME in EMA registry (52); ND = Not determined.

3.1.3 Reimbursement of hospital-exempt ATMPs in Germany

The reimbursement of medicinal products is dependent on the national regulations and the respective public health national insurance system of each MS. In the following section, the options for reimbursement of medicinal products in Germany are presented with special emphasis on reimbursement of hospital-exempt ATMPs. In order to get a medicinal product reimbursed by the Statutory Health Insurance in Germany, there are different evaluation procedures established involving different institutions. The way to go depends firstly on whether the medicinal product is going to be used in the outpatient or inpatient setting, and secondly whether it is classified as a medicinal product or a method in the framework of the reimbursement system. Figure 5 gives an overview of the different evaluation procedures establised in Germany for ATMPs centrally authorised and ATMPs nationally authorised under the HE.

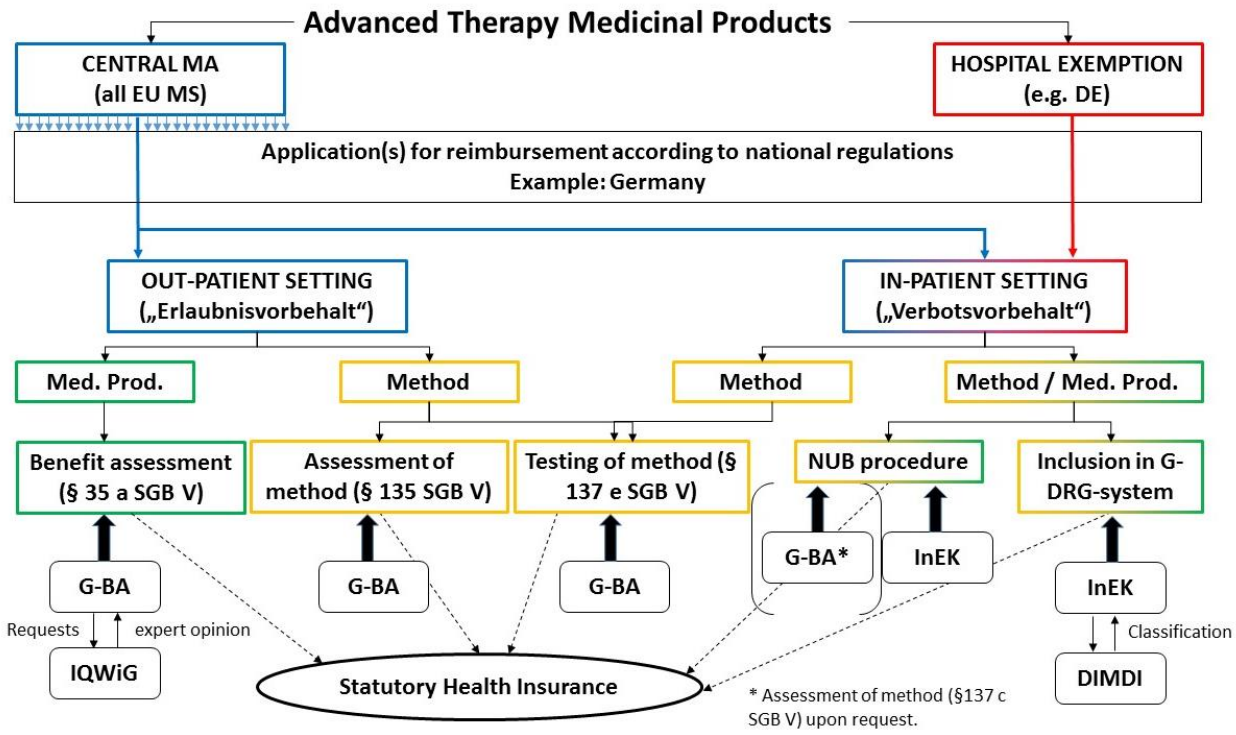


Figure 4: Reimbursement procedures available for ATMPs in Germany.

G-BA: The Federal Joint Committee; IQWiG: Institute for Quality and Efficiency in Health Care; SGB V: Book Five of the German Social Code; NUB: New examination and treatment methods; G-DRG: German Diagnosis Related Groups System; InEK: The Institute for the Hospital Remuneration System; DIMDI: The German Institute of Medical Documentation and Information.

Over 90% of patients in Germany are members of the Statutory Health Insurance funds (GKV) (61). Therefore, reimbursement by the GKV is of prime interest for authorisation holders of medicinal products. Private health insurances allow more flexibility for reimbursement, but are overall of less

importance due to the low numbers of insured persons. In Germany, the conditions for reimbursement of medicinal products by the GKV is regulated in Book Five of the German Social Code (SGB V) (62). According to Section 92 SGB V, the medicinal product must be evaluated for its benefit, necessity and cost-effectiveness by The Federal Joint Committee (*Gemeinsamer Bundesausschuss - G-BA*) in order to be reimbursable by the GKV. The G-BA is the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany and is under the statutory supervision of the Federal Ministry of Health (BMG) (63). Details on the methodological and scientific assessment procedures are contained in the Rules of Procedure of the G-BA (64).

The Act on the Reform of the Market for Medicinal Products (AMNOG) (65), which came into force on 1 January 2011, introduced new rules and procedures for the pricing of pharmaceuticals in Germany. Any new medicinal product with a new active ingredient having obtained a MA must undergo the benefit assessment according to section 35a SGB V conducted by the G-BA for setting the price for reimbursement by the GKV (see Figure 4). The G-BA can delegate the benefit assessment to the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the decision on the degree of the benefit in relation to a comparator treatment, prices for reimbursement by the statutory health insurance funds are set or negotiated.

In Germany, the options for reimbursement and the evaluation procedures depend on whether the medicinal products is used in the inpatient or outpatient setting (see Figure 4). In case of its use in the outpatient setting (e.g in a medical practice of a physician), any newly authorised medicinal with a new active ingredient must undergo the benefit assessment according to section 35a SGB V as mentioned above three months after it is placed on the German market. For example, the centrally-authorised ATMPs Glybera and Provenge are currently under benefit assessment according to Section 35a SGB V at the G-BA (66) (67). However, an ATMP can also be considered as an innovative examination and treatment method (*Neue Untersuchungs- und Behandlungsmethode - NUB*), if its use is part of a medical procedure rather than a stand-alone treatment. An example is the centrally authorised ATMP MACI (Matrix applied characterised autologous cultured chondrocytes), a TEP. According to the decision by the G-BA as of 20.06.2013, MACI is to be evaluated as a method according to Section 135 Abs. 1 SGB V instead of the benefit assessment according to Section 35a SGB V for medicinal products containing a new active substance (68). Method evaluation is performed in the subcommittee "Methods" of the G-BA. Importantly, a method applied in the outpatient setting is only eligible for reimbursement by the GKV, if positively evaluated for its benefit, necessity, and cost-effectiveness and explicit inclusion by the G-BA (so-called *Erlaubnisvorbehalt*).

In contrast, if a medicinal product is solely used in the inpatient setting (e.g. hospital), the G-BA only evaluates the benefit, necessity and cost-effectiveness as part of a method in case an application for evaluation according to section 135 c SGB V has been filed by entitled institutions such as the

National Association of Statutory Health Insurance Funds (*GKV-Spitzenverband*) (see Figure 4). In this case the G-BA may decide that a medicinal product as part of a medical treatment method is not any longer eligible for reimbursement by the GKV and excludes this method explicitly (so-called *Verbotsvorbehalt*). As an example, such an evaluation of a treatment method according to Section 135 c SGB V is ongoing for matrix-associated autologous chondrocytes implantation (ACI-M) of the knee joint (69). This is of relevance for certain chondrocyte products currently available under the HE in Germany, such the hospital-exempt ATMP co.don chondrosphere. Co.don chondrosphere is currently reimbursed as a NUB by the GKV for knee and hip joints (70). The application of matrix-associated autologous chondrocyte implantation in other joints including finger, shoulder, metatarsophalangeal of the big toe and the ankle have been excluded for reimbursement by the G-BA (see section 4 of the Directive Inpatient Methods as of 19.06.2014 (71).

Due to the prerequisites of Article 28 (2) of the ATMP regulation, ATMPs authorised under the HE are for use in the hospitals only (1). Therefore, only the reimbursement options for the inpatient setting are applicable to hospital-exempt ATMPs in Germany and thus further explained in the following section (see Figure 4).

For the inpatient setting, medicinal products are generally reimbursed within the case-based hospital payment system defined by the German Diagnosis Related Groups System (G-DRG-System). The G-DRG-System is based on the classification systems for diagnoses (ICD - International Statistical Classification Of Diseases And Related Health Problems) and the German Procedure Classification (*Operationen- und Prozedurenschlüssel – OPS*), which are both continously adjusted by the DIMDI (The German Institute of Medical Documentation and Information) (72). The Institute for the Hospital Remuneration System (InEK) is the responsible institution for establishing the lump-sum for each defined case within the DRG-System, which is updated yearly (73). However, most ATMPs are likely to increase the costs of the case-defined fee they are grouped to. As presented by the White Paper by Weber (2012) there are three options to compensate the increased costs of ATMP treatments in the inpatient setting:

- The NUB-Procedure
- Adjusting the G-DRG system rates
- Reimbursement within the testing of NUBs according to Section 137e SGB V

3.1.3.1 The NUB procedure

Based on section 6 (2) of the German Hospital Fees Act (*Krankenhausentgeltgesetz – KHEntgG*) (74), hospitals can apply for individual supplementary, non-DRG payments (so-called *Zusatzentgelt*) for NUBs, if they can demonstrate advantages of these new technologies such as increased treatment success and lower long-term costs (75). Application for NUB procedures can be submitted by the individual hospital to the InEK (see Figure 4). The electronic applications must be submitted until

the 31.10. each year. The InEK will evaluate the application, which includes assessment of whether the costs of the NUB are already sufficiently covered by the existing DRG case-based rates. Within 3 months (until the 31.01. of the following year), the InEK will reply to the applications by classifying the NUB with a status 1-4. If status 1 is obtained, the hospital may start negotiations with the local GKV for supplementary NUB reimbursement. Also a status 4 outcome will make it possible to start negotiations, although with less chance of success. Of note, reimbursement of the centrally authorised ATMP ChondroCelect has been based on a NUB4 status in Germany (76). The contractual agreements on the size of the supplementary NUB reimbursement are individually negotiated by each hospital with the local GKV. However, there is not a guarantee that negotiations are successful (77). Of note, the supplementary reimbursement is only limited for one year, which means that each year the hospital needs to resubmit the NUB application the InEK.

NUB reimbursement plays an important role for several hospital-exempt ATMPs in Germany. For example, NW Bio announced in its press release on 10.03.2014 (78) that its ATMP "DC-VAX-L" authorised under the HE in Germany on 21.02.2014 is eligible for NUB reimbursement according to the decision of the InEK:

"NW Bio also announced today that the German reimbursement authority (Institut Fur Das Entgeltsystem Im Krankenhaus, or InEK) has determined that DCVax-L treatments for glioma brain cancers are eligible to obtain reimbursement from the Sickness Funds (health insurers) of the German healthcare system. Applications for such reimbursement eligibility may only be submitted to InEK by German hospitals, not by a company. Six major hospital centers across Germany applied for such reimbursement eligibility for DCVax-L for glioma brain cancers. The amount and terms for such reimbursement will now be negotiated by NW Bio, the hospitals and the Sickness Funds over the coming months, and will be applied to patients case by case. In the meantime, patients may self-pay for DCVax-L." (78).

As was the case for DCVax-L, applications for NUB reimbursement can already start before the ATMP is authorised under the HE. Of note, the centrally authorised ATMPs ChondroCelect" indicated for cartilage repair in the knee, has also so far been reimbursed on a case-by-case basis via the NUB procedure (76).

3.1.3.2 Adjusting the G-DRG system

The NUB procedure is only a short-term, bridging solution to obtain reimbursement for innovative technologies such as ATMPs in the inpatient setting with a high uncertainty about the successful outcome of the negotiations for NUB reimbursement. The option to become an ATMP reimbursed within the G-DRG system, either as a supplementary fee or a unique DRG, offers a higher assurance of adequate reimbursement especially in the long-term (77) (75). Applications can be filed by certain eligible institutions such as hospitals or medicinal expert associations to the InEK each year until the 31.03. Once the ATMP has been included for DRG reimbursement, there is no need for the renewal of separate applications by each hospital to the InEK (77). The disadvantage is that the procedure is lengthly and can take several years before the new technology will have been integrated into the regular DRG-System.

3.1.3.3 Testing of examination and treatment methods according to Section 137e SGB V

The testing of examination and treatment methods in accordance with section 137e SGB V (62) is a relatively new procedure (since 01.01.2012), which allows the G-BA to initiate clinical studies for the "(…) testing [of] examination and treatment methods whose benefit has not yet been sufficiently proved, but which show potential as essential treatment alternatives." (79). The testing of methods according to section 137e is either initiated by the G-BA within the evaluation of a method according to section 135 or 137c SGB V or by the manufacturer upon application according to section 137e. Importantly, the manufacturer has only to pay part of the clinical study costs, while the other part may be reimbursed by the GKV (75). Therefore, this is an interesting option for ATMPs classified as methods, both in the in- and outpatient setting (see Figure 4).

All these three reimbursement options in the in-patient setting are available to ATMPs nationally authorised under the HE in Germany (see Figure 4). It is even advisable to combine those options, especially the application for the short-term supplementary reimbursement via the NUB procedure and the application for permanent inclusion in the G-DRG based hospital payment system. Of note, the reimbursement options in the inpatient setting are the same for centrally authorised and hospital-exempt ATMPs.

3.2 Implementation of the HE in the EU

In this chapter the implementation of the HE in the european MSs is investigated in terms of implementation of Article 28 (2) of the ATMP regulation /Article 3 No. 7 of Directive 2001/83/EC into the national legislations, the interpretation of HE eligibility criteria applied and the type and number of ATMPs supplied under the HE. Moreover, different views of individual MSs on the purpose of the HE are presented.

Taken together the report from the European Commission to the European Parliament and the Council, the public consultation on ATMPs and the survey of the Pharmaceutical Committee (7) (46) (80), it is possible to obtain some information on the implementation and interpretation of the HE in the EU MSs.

To complement the information available, I have searched for online information (preferably available in English) on the implementation of the HE provisions into national law, the interpretation of eligibility criteria and details on the application procedure on the websites of NCAs of the following MSs:

- Denmark (Danish Health and Medicines Authority, http://sundhedsstyrelsen.dk/en/)
- Finland (Finish Medicines Agency (Fimea), www.fimea.fi/en).
- Germany (Paul-Ehrlich-Institut (PEI), www.pei.de)
- Ireland (Health Products Regulatory Authority (HPRA), www.hpra.ie),

- The Netherlands (Medicines Evaluation Board, http://www.cbg-meb.nl/cbg/nl and Healthcare Inspectorate (IZG), http://www.igz.nl/)
- Spain (Spanish Agency for Medicines and Health Products (AEMPS), www.aemps.gob.es)
- Sweden (Medical Products Agency, http://www.lakemedelsverket.se/en)
- United Kingdom (Medicines and Healthcare Products Regulatory Agency (MHRA), http://www.mhra.gov.uk/)

Apart of a structured search for information on the HE or ATMPs available in the menue on each website, I have also searched for the terms "hospital exemption" and "advanced therapy medicinal product" on the individual websites of the NCAs using the available search button.

I addition to the PEI in Germany (information on the HE only available in German), the MHRA in the UK and the HPRA in Ireland have published user-friendly guidelines and guidance documents for ATMPs falling under the HE on their websites. Spain and the Netherlands also provide detailed information on the HE including application forms and FAQ documents, although only available in Spanish and Dutch, respectively. Table 4 gives an overview of the online information on the HE in Germany, Ireland, the Netherlands, Spain and the UK, including details on the type of the authorisation, the responsible NCA and the implementation into national law. As for Denmark, Sweden and Finland, the information available on the HE was limited and mostly provided in the national language.

Table 4: Information provided on the HE in Germany, UK, Ireland, Spain and the Netherlands.

	 **Germany**	 **United Kingdom**	 **Ireland**	 **Spain**	 **The Netherlands**
NCA	**PEI**	**MHRA**	**HPRA**	**AEMPS**	**IZG**
Online information	http://www.pei.de/DE/infos/pu/genehmigungen/atmp-4b-amg/antraege-genehmigung-4b-amg-atmp-node.html;jsessionid=4F97E313F1D06908E9ADCD4FFB1007AD.1_cid329 (available only in German!)	http://www.mhra.gov.uk/Howweregulate/Advancedtherapymedicinalproducts/Aboutadvancedtherapymedicinalproducts/#l2	http://www.hpra.ie/docs/default-source/publications-forms/guidance-documents/aut-g0091-guide-to-hospital-based-advanced-therapy-medicinal-products-v1.pdf?sfvrsn=6	http://www.aemps.gob.es/investigacionClinica/terapiasAvanzadas/home.htm (available only in Spanish!)	http://www.igz.nl/onderwerpen/geneesmiddelen/productie_en_distributie_geneesmiddelen/geavanceerde_therapie_atmp/ (available only in Dutch!)
Authorisation	Manufacturing authorisation and national authorisation if supplied to others.	Manufacturing license – Exempt advanced medicinal products (MeAT)	Manufacturing authorisation for manufacture of a hospital - exempt ATMP	National authorisation including manufacturing authorisation	Manufacturing authorisation specific for the HE
National law	Act amending the regulations on medicinal products and other regulations introducing Section 4b Medicinal Products Act (AMG), since 23.09.2009	The Medicines for Human Use (Advanced Therapy Medicinal Products and Miscellaneous Amendments) Regulations 2010, since 19.08.2010.	MedicinalProducts (Control of Placing on the Market) Regulations, 2007 - 2010 and specifically as amended by S.I. No. 3 of 2009, since 14.01.2009.	Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial since 14.06.2014	Geneesmiddelenwet (Article 40.3.d) (date of implementation unknown)

3.2.1 Implementation of the HE into the national legislation of EU MSs

The survey conducted by the Pharmaceutical Committee in 2011[5] showed that of the 28 participating MS there were 12 countries (CZ, Finland, Germany, Hungary, Ireland, Lithuania, Netherlands, Poland, Slovenia, Slovakia, Sweden, UK) that had stated implementation of the HE provisions and eligibility criteria into their national laws (80). In Austria, Belgium, France, Greece, Italy, Spain the implementation into national law were ongoing at that time. One would expect that now, almost seven years after the ATMP regulation came into force, most MSs have concluded the national transposition. While Austria (81), France, Spain as well as Portugal have implemented the HE provisions into their national laws in the meantime (82), in Italy, as an example known, the legal transposition of Article 28 (2) of the ATMP regulation / Article 3 No. 7 of Directive 2001/83/EC is still ongoing (83).

From the results of the survey of the Pharmaceutical Committee, it appears that several MS require a special manufacturing license/authorisation for ATMPs under the HE with focus on the quality of manufacturing and assessment of HE eligilibity criteria, but without an evaluation of the efficacy and safety of the ATMP in form of benefit/risk evaluation (80). As an example, the Netherlands requires the application for a HE to be submitted to the Health Care Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) that is the responsible authority for supervision and enforcement of pharmaceutical legislation instead of the Medicines Evaluation Board (CEB/MEB), wich is the NCA for the evaluation of medicinal products in the Netherlands (80). Finland also does not evaluate efficacy of ATMPs under the HE (32). In contrast, Germany requires in addition to the manufacturing authorisation by the local competent authority, an authorisation from the competent higher federal authority (the PEI) for supply of the hospital-exempt ATMP to others (see section 3.1 Implementation of the HE in Germany). Spain demands proof of efficacy and safety for hospital-exempt ATMPs by submission of quality, non-clinical and clinical data (82). Many MS, such as Austria (see Section 7 (6a) of the Austrian Medicinal Products Act) and Denmark (Part I (4a) Danish Medicines Act)[6] have implemented almost the exact wording of Article 28 (2) of the ATMP Regulation /Article 3 No. 7 of Directive 2001/83/EC into their national laws without any further guidances on the interpretation of the HE criteria (84) (81).

3.2.2 The interpretation of HE eligibility criteria in different EU MSs

In addition to the survey of the Pharmaceutical Committee, some useful information on the interpretation of the HE eligibility criteria can be deduced from the contributions of MSs to the public consultation on ATMPs (46), from the websites of some NCAs (see 3.2) and from the publication by

[5] Member States were invited to inform the Commission before 2 December 2011 (PHARM 598).

[6] Part I (4A.) of the Danish Medicines Act: "Notwithstanding section 3(1) and section 4(2), the Act does not apply to advanced therapy medicinal products which are prepared at a hospital in Denmark for a specific patient in compliance with the specific instructions of a doctor."

Cuende et al. (2014) (82) (46). Altogether there were six contributions by MSs and / or NCAs to the public consultation on ATMPs, including the Agencia Española de Medicamentos y Productos Sanitarios - AEMPS (Spain), the Superior Health Council of Belgium, the German Federal Ministry of Health and the PEI - (Germany), the Finish Medicines Agency - Fimea (Finland), the Medicines Evaluation Board – MEB (Netherlands) and the MHRA (UK). Taken together the information from the sources mentioned above, the HE criteria „non-routine" production is quite differenly construed in these MSs as is shown in Table 5. The Netherlands have defined specific criteria of how many patients may be treated by a hospital-exempt ATMP per order (max. 5 patients fulfills the criteria of individual preparation) and year (max. 10 patients), which already seriously limits the scale of production of ATMPs under the HE.

Table 5: Interpretation of the term „non-routine" production in Finland, Germany the Netherlands, Spain and the UK.

	"Non-routine" production
Finland	Not specified (production volume and number of patients treated are considered) (32).
Germany	Small scale production with medically justified deviations of routine processes or production of small quantities where full assessment is not yet possible (see Section 4b (1) AMG (9) (case-by-case decision)
Netherlands	ATMP prepared on a small scale, prepared from autologous cells or prepared from allogenic cells specifically for an individual patient (85) max. 10 patients per year, 5 patients per order (85);
Spain	Occasional and non-industrial manufacturing (86) (46) (case-by-case decision)
UK	Dependent whether it is considered the same product and scale and frequency of the preparation of the specific product (87) (case-by case decision).

Not only is the term "non-routine" production of a hospital-exempt ATMP differently interpreted in these MSs, but also conditions for the authorisation and manufacturing appear to be divergent. Spain limits the authorisation of ATMPs under the HE to hospitals only (86) and as such is in line with the originally proposed proposed HE by the European Commission (33). However, several hospitals can hold HE authorisations for the same ATMP that is manufactured by an external manufacturer (82). In Germany, the HE authorization is usually issued to the manufacturer, who is then allowed to distribute the authorised product to different hospitals. In this case, the different hospitals themselves do not need to hold separate HE authorisations. No room for interpretation leaves the fact that hospital-exempt ATMPs must only be used within the MSs of manufacturing. This means that import and export of ATMPs under the HE is not possible.

Also the purpose of the HE is perceived and interpreted differently in some MS. This is shown exemplarily for Finland, Germany, the Netherlands, Spain and the UK in Table 6. Finland and the Netherlands consider the HE as an opportunity for early clinical development prior to CTs and and as a form of experimental clinical treatment outside of CTs, respectively (32) (85) (82). According

to the contribution to the public consultation on ATMPs, the HE is mainly valued as a tool to support the transition from non-routine to routine production and thus eventually towards a central MA (46). Clinical data generated from the application of hospital-exempt ATMPs are considered to be supportive for the future clinical evaluation for a central HE (personal communication with the innovation office at the PEI). Moreover, for specific cases, the HE is also viewed as a permanent alternative to the central MA. For example, a product consisting of autologous cells but intended for non-homologous use classifies as an ATMP according to Article 2 (1) c of the ATMP regulation. If in this case manufacturing and use of this product would be confined to the same institute of an hospital or even to the same surgical theatre, and if manufacturing and application is performed by the same person, this would be an example of an ATMP for which the HE would be a permanent alternative to the central MA. The UK views the HE as an regulatory option for small scale manufacturing and application of unlicensed ATMPs comparable in some respects to their "Specials" scheme according to Article 5 (1) of Directive 2001/83/EC, another exemption from a MA not only restricted to ATMPs (88).

Table 6: Scope and purpose of the HE in Finland, Germany, the Netherlands, Spain and the UK.

	Scope of the HE
Finland	Early clinical development (82) (46); same requirements as for first in man clinical studies (32).
Germany	Transitional authorisation supporting product and clinical development for future central marketing authorisation application (MAA) (46); Real alternative to the central MA for specific products (46).
Netherlands	Small scale clinical use as experimental treatment (46), esp. for patients not eligible for CT (82).
Spain	Permanent alternative to central MA (82), especially for products "historically" used in Spain (80).
UK	Supply of unlicensed ATMPs at small scale and with developmental nature of activity (88).

3.2.3 Number and type of ATMPs that are on the EU market

According to the EMA surveys mentioned in the report by the European Commission of 28 March 2014 (7), there have been 31 ATMPs legally on the market according to national provisions prior before the application of the ATMP regulation from 30.12.2008 (1). Approximately half of these products were chondrocyte-containing products. The report by the European Commission summarises that as of April 2012, approximately 60 products that classify as ATMPs were exempted from the central MA in the EU MSs (7). These exemptions are either granted under Article 28 (2) of the ATMP regulation / Article 3 No. 7 of Directive 2001/83/EC or Article 5 (1) of Directive 2001/83/EC (1) (8).

According to the outcome of the survey conducted by the Pharmaceutical Committee (80), ten countries stated that ATMPs were legally on their market of which six countries (Denmark, Finland, Germany, Netherlands, Italy and Spain) stated that these fall under the HE provisions (80). Apart of the centrally authorised ATMP ChondroCelect, which was in fact the first ATMP that obtained the central MA in 2009, other ATMPs that were stated to be legally on the market in 2012 -whether under the HE or otherwise authorised[7] - were mainly autologous chondrocyte products. Also, products containing mesenchymal stem cells for Graft versus Host disease and limbal stem cells, as well as skin keratinocytes were on the market in Sweden and Spain, respectively (80). In general, it appears that most of the ATMPs that were reported by the MSs to fall under the HE provisions had already been on the market prior to the application date of the ATMP regulation (30.12.2008). Spain for example explicitely stated that for the present, only those products will be considered for the HE that have been „historically" used in Spain before this exemption will also become available to new products (80). Other MSs such as the Czech Republic, Germany and Italy declared that products that had been on the market before the provisions of the ATMP regulation became effective are undergoing evaluation for HE or the application for a central MA is pending.

In Germany, a transitional period defined in Section 144 (2-3) AMG was granted to products that had been on the market on 23.09.2009 (the date the German national provisions of the HE came into force) (9). These transitional provisions allowed those products to stay on the market, if an application for authorisation pursuant to Section 4b (3) AMG was submitted until the dates specified[8]. Access to the German market was to be continued until the evaluation of the HE was decided upon. Ofe note, it took approximately three years for the first 4b authorisation to be granted in Germany (see Table 3).

According to the PEI registry, there are currently seven ATMPs nationally authorised under the HE in Germany, many of which are TEPs that had been on the market before the application of the ATMP regulation (51). However, the result of my online searches on the websites of other NCAs was that information on the types of ATMPs currently marketed under the HE in other EU MSs was not readily available. Some information with this respect can only be deduced from the information of the Pharmaceutical Committee survey (80) and the public consultation on ATMPs (46). For example, the MHRA states in it´s contribution to the public consultation that currently one ATMP is authorised under the HE scheme. However, no further information is given on the type of product. Clearly, there is a lack of transparency on the availability of ATMPs under the HE.

Some of the products that had been on the market before the ATMP regulation applied proceeded to the application of a central MA (see Table 7). According to the report by the European Commission

[7] The UK reported 18 authorisations for ATMPs under the UK´s Specials scheme according to Article 5(1) of Directive 2001/83/EC.

[8] The deadline for the submission of the application for the HE according to Section 4b(3) AMG was the 01.08.2010 for GTMPs and SCTMPs and the 01.01.2011 for TEPs.

(7), which covered the time period until 30.06.2013, five of the ATMPs that a central MAA was filed, were on the EU market before the 30.12.2008. From the information that is available by the survey of the Pharmaceutical Committee (80), the Agendas, Minutes and Monthly reports of the the Committee for Advanced Therapies (CAT) (89) and the section „Withdrawn applications“ and „Medicines under evaluation“ on the EMA website (90) and the information available from the companies (91) (83) and presentations (57), it is possible to identify four of these products to be MACI, Hyalograft C, co.don condrosphere and Holoclar. The limbal stem cell products Holoclar has been applied since 2001 in Italy and is still being applied in several Hospital centers (83). What all these four products habe in common is that they classify as TEPs. Of these products one has received approval (MACI), one was withdrawn (Hyalograft C) and two products are still under evaluation (co.don chondrosphere and Holoclar) (see Table 7). Notably, co.don chondrosphere was granted the first authorisation under the HE in Germany on 12.12.2013 according to the registry of the PEI (see Table 3), with the central MAA still pending (see Table 7). Holoclar is still being used in Italy in several Hospital Centers, but not under the HE, as the legal provisions of Article 28 (2) of the ATMP regulation / Article 3 No. 7 of Directive 2001/83/EC have not yet been implemented in Italy (83). Since the time of the European Commission report was compiled on 30 June 2013, there have been three more central MAAs for ATMPs received by the EMA. An overview of all the central MAAs received by the EMA for ATMPs up to October 2014 are provided in Table 7.

Table 7: ATMPs following the centralised procedure at the EMA (as of 09.2014)

Name	ATMP	Submission	Approval	Withdrawal	Under evaluation	Prior market access**
ChondroCelect (TiGenix NV) BE*	TEP	01.06.2007	05.10.2009			No
Contusugene Ladenovec Gendux (Gendux Molecular Limited) IRE	GTMP	02.07.2008		12.06.2009		ND
Cerepro (Ark Therapeutics Gropu plc)	GTMP	28.11.2008		08.03.2010		ND
Glybera (UniQure Biopharma B.V.) NL*	GTMP	23.12.2009	25.10.2012			No
OraNera (CellSeed Europe Ltd) UK	TEP	01.06.2011		14.03.2013		ND
MACI (Genzyme Europe B.V.) NL	TEP	01.09.2011	27.06.2013			Yes
Provenge (Dendreon UK Limited) UK	sCTMP	30.12.2011	06.09.2013			No
Hyalograft C (Anika Therapeutics Inc.) US	TEP	28.02.2012		14.01.2013		Yes
co.don chondrospheres (co.don AG) DE*	TEP	12/2012			X	Yes
Holoclar (Chiesi Farmaceutici) IT	TEP	04/2013			X	Yes
Heparesc (Cytonet GmbH&Co KG) DE	ND	01/2014			X	ND
Zalmoxis (MolMed SpA) IT	ND	03/2014			X	ND
talimogene laherparepvec (Amgen)	ND	03/2014			X	ND

ND = Not determined

*SME status according to the Micro-, small- and medium-sized-enterprise (SME) register at the EMA website (52)

** Product on the EU market according to national provisions before the application of the ATMP regulation on 30.12.2008.

3.3 The HE as compared to the other early access options available for ATMPs in the EU

The HE is a specific exemption for ATMPs from obtaining the central MA. The following section shows, which other regulatory options exist for the access to unauthorised ATMPs and how they compare to the HE. As was shown in the previous chapters, the HE is considered a regulatory option to faciliate (early) access to unauthorised ATMPs in individual EU MSs before a central MA is obtained (transitional option) or as a permanent alternative to the central MA. However, the regulatory framework of the EU foresees also other options for (not yet) unauthorised medicinal products to be made accessible to patients, including CTs based on Article 3 No. 3 Directive 2001/83/EC (8), compassionate use (CU) programmes based on Article 83 of Regulation (EC) No 726/2004 (10) or on the basis of Article 5 (1) Directive 2001/83/EC (Named patient use) (8). These other options for early access to unauthorised medicinal products are also available for ATMPs without a central MA (see Figure 5). Of note, CTs and CU programmes are destined for the treatment of a defined cohort of patients, while the Named Patient Use based on Article 5 (1) of Directive 2001/83/EC and the HE are limited to use by individual patients.

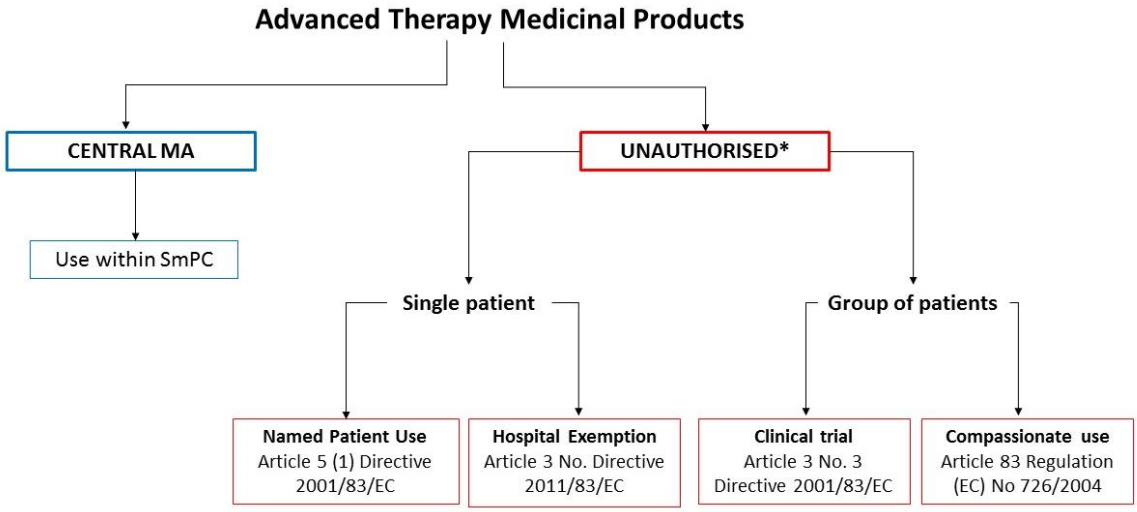


Figure 5: EU regulatory framework for early access to unauthorised ATMPs [Figure modified from O'Meara (92)]. *unauthorised = without a EU central MA in compliance with the ATMP regulation.

The above mentioned additional european provisions for early access to unauthorised medicinal products are implemented into the German AMG (9) in Section 21 (2) Nr. 2 (CTs), Section 21 (2) Nr. 6 (CU programmes) and to some extend in Section 73 (3) AMG (in parts implementation of Article 5 (1) of Directive 2001/83/EC Named Patient Use). A comparison of the main aspects of the HE as compared to the other early access options available is presented in Table 8.

3.3.1 The HE compared to early access to unauthorised ATMPs via CTs

The most standardised and preferred way how patients get early access to new pharmaceuticals such as ATMPs under development and not yet holding a marketing authorised in the EU are CTs. CTs in the EU are regulated by the Directive 2001/20/EC (CTs Directive) as amended (23). In Germany, the european provisions of the CTs Directive are implemented in the German AMG, sixth chapter, Section 40-42b (9) and in the supplementing Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trial on medicinal products for human use (*GCP-Verordnung* – GCP-V) (49). Medicinal products undergoing CTs are exempt from the obligation to obtain a MA according to Section 21 (2) Nr. 2 AMG, but they require approval from the competent higher federal authority, which in case of ATMPs is the PEI (see Section 77 AMG). In addition, a favourable opinion of the competent ethical committee is required before the start of a CT (see Section 40 (1) sentence 2 AMG). In contrast to the HE which is an exemption from the MA specific to ATMPs, CTs (Phases I-III) are applicable to any medicinal product not authorised yet. Also, there is no restriction on the investigation of certain diseases as is the case for medicinal product of CU programmes (see Table 8).

Information on CTs is available to the public on the EU Clinical Trials Register (93). The main differences to the HE is that the treatment of patients within CTs is defined for a specified group of patients (cohort). Only, if all inclusion criteria for the study are met, may a patient participate in the CT. However, this also means that other patients not fulfilling all the criteria are excluded from receiving promising treatment witin the context of a CT. In such cases, the HE may offer patients access to ATMPs outside of CTs. DCVax-L, a cancer vaccine indicated for a certain type of brain cancer (glioma), is currently undergoing Phase III CTs in Germany and the UK for newly diagnosed Glioma multiforme (GBM) (94), which is the most severe grade of gliomas. At the same time DCVax-L is available under the HE to patients with different grades of glioma, both newly diagnosed and recurrent (95).

3.3.2 The HE compared to early access to unauthorised ATMPs via CU programmes

The legal basis for CU programmes is Article 83 of Regulation (EC) No 726/2004 (10). As stated on the EMA website on CU,

"The objectives of Article 83 are to:

- facilitate and improve access to compassionate-use programmes by patients in the EU;
- favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicines;
- increase transparency between Member States in terms of treatment availability." (96).

Although contained in the Regulation (EC) No 726/2204, implementation of CU programmes is not binding for the european MS (see Article 83 (1) of Regulation (EC) No 726/2004). In Germany, the legal basis for CU programmes is Section 21 (2) Nr. 6 AMG. Details of the requirements of CU

programmes are contained in The Ordinance on Medicinal Products for Compassionate Use (*Arzneimittel-Härtefall- Verordnung - AMHV*) as of 14 July 2010 (97).

CU programmes are aimed to making not yet authorised medicinal products under development available to "[…] patients with a chronically or seriously debilitating disease or whose disease is considered to be life- threatening, and who can not be treated satisfactorily by an authorised medicinal product." (see Article 83 (2) sentence 1 Regulation 726/2004)[9]. If these conditions are fulfilled, CU programmes should also be applicable to ATMPs. In contrast to CU programmes, Article 28 (2) of the ATMP regulation does not restrict the HE of ATMPs to certain disease conditions and unmet medical need, although one can find similar demands expressed also in the context of the HE, for example in contributions to the European Commission public consultation of ATMPs (46).

CU programmes are intended for limited period until a MA is obtained for this medicinal product. Therefore, the medicinal products made available within CU programmes must be either under investigations in CTs or a marketing authoristion application must be ongoing (see Article 83 (2) of Regulation (EC) No 726/2004) (10). Although the HE for ATMPs is also seen as a temporary option for unauthorised ATMPs to facilitate clinical development to eventually transition to the central MA, the european provisions of Article 28 (2) of the ATMP regulation do not stipulate that CTs or a central MAA must be ongoing. On the contrary, the prerequisiste of non-routine production for hospital-exempt ATMPs could even exclude the routine production required for a central MA. In this sense, some MS acccept the HE to be a permanent alternative to the central MA..

According to the guidance on CU in Germany, the safety and efficacy of medicinal products for a CU programme need to be normally shown by confirmatory clinical studies (Phase III) (98). In contrast, ATMPs supplied under the HE may be at an earlier stage of clinical development, depending on the view of the respective MS. Due to safety reasons, completion of at least Phase I for hospital-exempt ATMPs is expected in Germany (personal communication with the Innovation office at the PEI).

As for ATMPs available under the HE in Germany, there is also a registry for CU programmes for biological medicinal products available on the PEI website (99). According to this registry, there is currently no ATMP available under a CU programme in Germany.

The data from medicinal products supplied within CU programmes may be used to improve the understanding of the efficacy and safety profile, but under no circumstances must CU programmes be be used as an alternative to CTs (98). Similarly, the HE can be considered as a transitional national authorisation outside of CTs until a central MA is achieved. In this case the knowledge gained from

[9] According to Article 83 (2) of Regulation (EC) No 726/2004, only medicinal products that are eligible for the central marketing authorisation procedure are to be considered for use under compassionate use (see Article 3 (1-2) in conjunction with Annex I of Regulation (EC) No 726/2004) (10).

the application of ATMPs under the HE could be supportive for the central MA dossier and also for the design of CTs. Of note, "- the role of data generated from the use of a product under the hospital exemption in the context of an application for a marketing authorisation." was declared an open issuein the European Commission report on ATMPs (7) based on contributions of the the public consultation on ATMPs (46), as this might be differently viewed in the MSs and also there has so far been no clarification whether such data will be accepted for a central MAA by the EMA.

In Germany, one crucial difference between CU programmes and the HE for ATMPs are the costs. According to Section 21 (2) Nr. 6 AMG, the medicinal product must be provided free of charge when supplied within a CU programme. In contrast, hospital-exempt ATMPs may be reimbursed by the German statutory health insurance (see section 3.1.3), an important benefit for SMEs to continue product development towards a central MA.

3.3.3 The HE compared to Article 5 (1) of Directive 2001/83/EC (Named Patient Use)

Article 5 (1) of Directive 2001/83/EC reads as follows:

"A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility." (8).

Similar to the HE for ATMPs, the Named Patient Use based on Article 5 (1) of Directive 2001/83/EC is restricted to individual patients and for use under the direct responsibility of the medical prescriber. According to Article 28 (2) of the ATMP regulation, hospital-exempt ATMPs should be prescribed by a medical practitioner, wherease prescription of medicinal products for the named patient may be less restricted to health-care professionals (e.g. in the UK authorised health-care professionals include doctors, dentists and supplementary prescribers according to the Guidance on the UK´s arrangements under the hospital exemption scheme) (88). A difference to the HE is the fulfillment of "special needs" required for medicinal products supplied under the named patient use based on Article 5 (1) of Directive 2001/83/EC. For example, in Germany the supply of imported medicinal products under Section 73 (3) AMG for individual patients, is only possible if no alternative medicinal product is available in Germany. Another important difference to the HE is the possibility of import of a medicinal products under Article 5 (1) of Directive 2001/83/EC. Import of hospital-exempt ATMPs from other MSs is not possible, because their use is restricted to the MS of manufacturing. Importantly, Article 5 (1) does not even specify whether the medicinal product must be authorised at all. As an example, the UK also allows the import and supply of medicinal products (including ATMPs) not licensed elsewhere under Article 5 (1) within their "Specials" scheme (100). The Netherlands allow treatment with unregistered products under the "Doctor´s Declaration", which must be authorised by the IGZ (101), but only if no alternative registered products are available in

the Netherlands. For example, the supply of a medicinal product under a "Doctor´s Declaration" is possible, if a patient may not be eligible for participation in a CT.

In Germany, the european provisions of Article 5 (1) of Directive 2001/83/EC are considered to be at least partially reflected in Section 73 (3) AMG (102), which allows import of finished medicinal products not authorised in Germany from other EU MSs, States of the EEA or Third Countries (9). Importantly, the imported medicinal products must be legally on the market of the exporting country (see Section 73 (3) No 2 AMG). Moreover, there must not be any other authorised medicinal product with the same active and comparable strength for the indication available in Germany (see Section 73 (3) Nr. 3 AMG). The supply of completely unlicensed medicinal products in Germany outside of the existing exemptions of Section 21 (2) AMG (e.g CTs, CU programmes), is only possible further to an attempt of an individual medical treatment (*Individueller Heilversuch*) within the sope of the medical therapeutic freedom (*Therapiefreiheit*), which is under the exclusive responsibility of the doctor (103). Not being regulated in the German pharmaceutical legislation, the legal basis of a *individueller Heilversuch* is Section 34 "Necessity" of the German Criminal Code (*Strafgesetzbuch-StGB*) as a "justified emergency" (104). *Individuelle Heilversuche* in Germany are not limited to certain medicinal products and should in principle also include ATMPs. Supply of ATMPs based on Section 73 (3) AMG or as a *individueller Heilversuch* may present a life-saving option for individual patients with high need of innovative treatments. However, these are exceptional cases and does not present a regulatory option comparable to the HE, especially because reimbursement by the German statutory health insurance funds is only possible under specific circumstances on a case-by-case decision.

Table 8: Comparison of early access options for patients to unlicensed ATMPs as exemplified for DE.

	HE authorisation	**Named Patient Use**	**CU Programme**	**CTs**
Legal basis (EU)	Article 28 (2) Reg. (EC) No 1394/2007	Article 5 (1) Dir. 2001/83/EC	Article 83 Reg. (EC) Nr. 726/2004	Article 3 Nr. 3 Dir. 2001/83/EC
Patients	Single/individual	Single/individual	Group	Group
Medicinal products	ATMPs only	Any	Limited acc. to Article 3 (1-2) Reg. (EC) No 726/2004	Any
Disease	Any	Special need	chronically or seriously debilitating or life-threatening disease	Any
Import	No, the ATMP must be manufactured and used in the same EU MS	Import not excluded acc. to Article 5 (1) Dir. 2001/83/EC	Possible	Possible
Legal basis (DE)	Section 4b (3) AMG	Section 34 StGB (justified emergency) / Section 73 (3) AMG (import of licensed medicinal product)	Section 21 (2) Nr. 6 AMG	Section 21 (2) Nr. 2 AMG
Legal basis of application (DE)	Section 21 a (2-8) AMG	None	Section 3 AMHV	Section 40 (1) AMG and Section 7 GCP-V
Approving authority (DE)	PEI	Local competent authority	PEI or BfArM	PEI or BfArM
Clin. Development (DE)	After completion of Phase I	Not specified	Phase III / ongoing MAA	Phase I-III
Reimbursement (DE)	Possible	Possible (but strictly case-by-case)	No	Only the standard treatment costs are reimbursed)
Validity (DE)	Limited (renewable) or permanent	Only single cases	Max. one year, (renewable)	Temporary (duration of CT)
Information of the public (DE)	PEI registry on ATMPs (51)	No	PEI registry on CU programmes (99)	EU Clinical Trials Register (93)
Costs of application (DE) acc. to fee ordinance (105)	4.250 – 17.000 EUR (105)	Not specified (case-by-case)	Not determined	4.000 – 5.000 EUR (105)

4 DISCUSSION

4.1 The HE, a regulatory option for unauthorised ATMPs

Before the ATMP regulation came into force at the end of 2007 and applied from 30.12.2008, products then classified as ATMPs were already on the EU market under national legal provisions, which in many cases meant that the products were distributed under manufacturing authorisations in the respective MSs. When establishing the new regulation for ATMPs, two of the aims were to harmonise the EU market for ATMPs and to protect public health by having the same standards for the assessment of quality, safety and efficacy of ATMPs among the EU MSs. This was mainly to be achieved by making the central MA mandatory for ATMPs and by establishing a specialised committee at the EMA, the CAT, which consists of experts for these innovative therapies from throughout the EU (106).

Notably, the scope of the ATMP regulation includes products "(…) which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process (…)." (see preamble 6 of the ATMP regulation) (1). Already the proposal of the ATMP regulation by the European Commission included the HE in Article 28 (33), which indicates that from early on an exemption for ATMPs produced on a non-routine basis in hospitals was foreseen by the legislators. Originally, the intention was to limit this exemption to ATMPs produced and used in hospitals only. It was due to the amendments during the legislative process that the HE was recomposed in its current version in Article 28 (2) of the ATMP regulation. Importantly, Article 28 (2) of the ATMP regulation amends in turn Article 3 of the Directive 2001/83/EC, with the result that MSs had to implement the legal provisions of the HE into their national laws. The current version of Article 3 Nr. 7 of Directive 2001/83/EC allows room for interpretation as some of the terms are not clearly defined or further explained in the European provisions. Apparently this lowest common denominator was decided upon during the legislative procedure of the ATMP regulation to accommodate all MSs views and demands on this exemption (34). It is this ambiguity of Article 28 (2) ATMP regulation that causes the heterogeneous application of the HE among the different EU MSs. As a consequence, the aim to harmonise the european market for new and existing ATMPs has to some extend been impeded by the different interpretation and application of the HE among the EU MSs, which in turn may also have an impact on the development of ATMP as well as patient´s access to innovative therapeutic approaches provided by ATMPs. Then why does an exemption from the central MA is needed after all?

Almost six years since the ATMP regulation came into effect on 30.12.2008, there have only been 13 central MAAs for ATMPs submitted to the EMA in total (see Table 7). Of these products only five had been on the EU market under national provisions when the ATMP regulation started to apply. This means that of the 31 existing ATMPS that were reported by the European Commission

to have be on the EU market under national provisions (7), only a minor fraction has so far managed to file a central MAA and not one single of these products managed to obtain the central MA within the transitional period set by Article 29 of the ATMP regulation. Notably, of the four ATMPs having obtained MA approval so far, only one product (MACI) had previously been on the EU market. This indicates that the aim of the ATMP regulation to harmonise the (existing) market of ATMPs in the EU by introducing a common regulatory approach to AMTPs and at the same time fostering novel therapeutic approaches has not been very successful so far.

The requirements for a central MA now mandatory for ATMPs are high, probably too high for many of the developers of ATMPs, which mainly consist of SMEs, hospitals and academia. According to Maciulaitis et al. (2012) big pharmaceutical companies make up less than 2 % of the sponsors of CTs for ATMPs (6). The uncertainty of return on investment (ROI) due to often limited patient numbers and regulatory challenges probably makes the development of ATMPs less attractive for Big Pharma. Thus the field of ATMPs is dominated by enthusiastic and science-driven companies and research groups, who often lack the resources in terms of investment, personnel and regulatory expertise to develop a product through to a central MA. Also, many ATMPs are developed for rare diseases to meet the medical need of only a limited number of patients, which makes it difficult to conduct confirmatory CTs required for a central MAA. Moreover, the scientific challenges due to the nature of these innovative therapeutic approaches make the development of ATMPs in compliance with the established standards for small molecule medicinal products (e.g. for GMP) rather difficult (30) (107).

Although incentives for the development of ATMPs were established in chapter 6 of the ATMP regulation (1), they do not seem to be sufficient to support successful development of ATMPs. Also, some of the incentives such as the certification procedure for the quality and non-clinical data by the CAT are open only to registered SMEs (see Article 18 of the ATMP regulation), neglecting the fact that also hospitals and academia are among the applicants who would benefit from it.

Considering the increasing numbers of HEs granted to ATMPs in Germany, it becomes clear that many of the applicants have not yet achieved transition to the central MA. The transitional period set by the ATMP regulation for existing ATMPs was too short to meet all the requirements of a central MA, but also developers of new ATMPs are among those that may benefit from the HE (see section 4.3).

4.2 The HE from a regulatory perspective

The controversy about the details and scope of the HE during the legislative procedure of the ATMP regulation is reflected in today´s situation of different national interpretation of the criteria used in Article 28 (2) of the ATMP regulation such as “non-routine production” as is presented in section 3.2.2. Also other terms are differently construed in some MS than in others and thus may change the scope of the HE. As was shown for Germany, the term “hospital” used in Article 28 (2) of the ATMP

regulation was replaced by "specialised facility for health care" for the implementation of the european provisions into Section 4b AMG. Thus, administration of hospital-exempt ATMPs in Germany is not limited to use in hospitals only, but also allows for use in outpatient setting such as specialised medical practices. In other MSs such as Spain the use of ATMPs under the HE is strictly limited to hospitals only (82). The differences in the interpretation especially of the eligibility criteria of the HE may lead to differences in the access to certain products among the MSs. For example, the Netherlands have a very narrow definition of "non-routine" production, which allows treatment of a maximum of 10 patients per year only and in Spain industrial production is generally excluded for ATMPs under the HE (see section 3.2.2). Germany allows "routine manufacturing procedures" providing that medically justified variations according to the individual patient are introduced (see Section 4b AMG). This may to lead to differences in the acceptance of ATMPs under the HE based on the manufacturing processes among the MSs. Giving a practical example, a personalised tumour vaccine based on RNA is tailored to the sequences of tumour markers which are individually determined for each patient (108). Although the production processes to manufacture the RNA may follow a standardised protocol and may also involve industrial processes, the differences in the sequence may justify the individuality of the product and thus eligibility of this tumour vaccine for the HE, providing the product is classified as an ATMP.

Differences among the MSs exist also in the extend of evaluation of ATMPs under the HE. While many MSs primarily assess the products in terms of the quality of the production under a specialised manufacturing licenses issued to ATMPs under the HE, assessment of efficacy and safety based on non-clinical and clinical data is required in other MSs such as Germany and Spain (82). Still, although a benefit/risk evaluation of ATMPs under the HE to be supplied to others is carried out by the PEI in Germany (50), the requirements on the respective data are still less demanding and allow more flexibility (e.g. date from clinical experience outside of CTs) than for a central MA (see section 3.1.1). Furthermore, also the intention and purpose of the HE may be differently perceived by the MSs. Finland, for example, considers the HE to facilitate early clinical development similar to First-in-man studies (32), while Spain requires full evaluation of non-clinical and clinical data to support a HE application (82) and Germany normally expects at least completion of Phase I or other clinical experience. As a consequence, inefficient or even unsafe ATMPs could potentially enter a market under the HE in MSs with lower data requirements, while in another MSs with higher requirements such a product would not be granted the HE. Thus, different standards of ATMPs in terms of safety and efficacy may be available in the EU MSs depending on the extend of evaluation within the HE and also the expert knowledge for these type of products available in the MS concerned.

Apparently, also the term "specific quality standards" has been differently interpreted in some MS as it was a major issue presented by the contributions to the public consultation on ATMPs (46). However, Article 28 (2) of the ATMP regulation clearly states that ATMPs that are exempted via the HE from the obligation to obtain a central MA must meet the equivalent specific quality standards

as centrally authorised ATMPs. This statement in fact leaves little room for interpretation by the MSs and implies that also ATMPs under the HE must be manufactured in compliance with the general rules of GMP and additional standards specified for ATMPs, such as contained in Annex 2 of the GMP guidelines (14) and the scientific and regulatory guidelines available. Compliance with GMP is very challenging for the manufacturing of many ATMPs due to small sample size, short shelf-lifes and also appplicability of analytical methods (30) and and according to Närhi and Nordström (2014) constitutes a major regulatory burden to cell-based therapeutic products (109). Therefore, it may well be that some MSs allow more deviation from the expected GMP standards than others. Also, pharmacovigilance including follow-up of safety and efficacy measures and traceability requirements as defined in Article 14 and 15 of the ATMP regulation should apply to hospital-exempt ATMPs. This generally means that although exempted from the obligation of the central MA, safety aspects as regards the manufacturing and application of the hospital-exempt ATMPs should be the same as for centrally authorised ATMPs. However, Reischl and Ferreira (2013) raise the legitimate concern "(…) how an authorisation limited to manufacturing can encompass or respond the the required pharmacovigilance obligations." (110).

A non-controversial condition of the HE according to Article 28 (2) of the ATMP regulation is that manufacturing and use of hospital-exempt ATMPs must take place in the same MS. Thus neither import of ATMPs manufactured under the HE from another MS nor export of ATMPs produced under the HE to other MSs is possible.

In addition to the above mentioned terms and conditions of Article 28 (2) of the ATMP regulation, there may be other requirements contained in the national legal provisions of the HE of the respective MS. As shown for Germany in section 3.1.1.4, further details regarding the national authorisation of hospital-exempt ATMPs pursuant to Section 4b (3) AMG, including validity, reporting obligations, the legal basis for the data requirements and grounds for withdrawal and revocation of the authorisation are given. Moreover, the innovation office at the PEI offers regulatory advice for the HE procedure in addition to detailed guideances and a registry with hospital-exempt ATMPs (42). My searches for similar details on the application procedure, guidances and registries in other MSs showed that information on the HE is limited and is mostly available in the language of the MS concerned. Importantly, registries similar to the one available on the PEI website are not readily available in the MSs that were included in my searches. For a complete picture of the different national requirements and also the numbers of ATMPs available under the HE, individual enquiries at the NCAs in each MS would have been necessary, but this was out of scope of this master thesis.

Overall, the HE is considered as a useful tool for the development of innovative therapies by most of the NCAs taking part in the public consultation on ATMPs (46). However, the main issue was the lack of harmonisation of the interpretation and scope of the HE among the MSs. The liegitimate concern is that this could create a similar situation of a fragmented and heterogenous market for ATMPs as had been the case before the ATMP regulation came into force. However, as controversy

about the scope and application of the HE was already obvious during the legislative procedure of the ATMP regulation, it may well be that such issues are difficult to solve as the healthcare systems may operate very differently in the MSs. From my point of view, the lack of transparency especially on the availability of ATMPs under the HE is also a major issue, which could be solved by establishing a central registry of hospital-exempt ATMPs in the EU. Another possibility to increase the transparency would be to include the manufacturing authorisations issued for ATMPs under the HE into the EudraGMDP database (111).

4.3 Impact of the HE on the development of ATMPs

According to Maciulaitis (2012), the majorities of entities currently acting as sponsors of CTs for ATMPs are either SMEs, academia or charitable organisations (6). As is shown in Table 3 of this thesis, also the majority of currently registered ATMPs in Germany are provided by SMEs or other local enterprises, which holds especially true for ATMPs authorised under the HE. However, even if not registered in the SME database provided for by the EMA (52), a company can still belong to this group and may be limited in size. The common nominator for the majority of developers of ATMPs is the lack of resources for investment, personnel and regulatory expertise. However, the intentions to develop an ATMP may be very different depending on the overall aim. Even though SMEs are limited in sizes and resources, the focus is to eventually market a product, which will render ROI. A less commercialised view is present in academia, hospitals, research institutions and charitable organisation. In this group the approach to the development of ATMPs is science-driven and with the primary aim and often genuine interest to provide therapies to certain patient groups with unmet medical need often associated with rare diseases. As became obvious by the contibutions to the public consultation on ATMPs, the views on the HE are indeed different among the developers of ATMPs. The industry´s position as for example represented by the contribution of the European Pharmaceutical Enterprises (EBE) or the Alliance for advanced therapies (AAT) critisize that the broad application of the HE impedes the development of centrally authorised ATMPs by creating a second market for ATMPs provided for under the HE. Although acknowledging the HE as an important option for specific products, especially intended for patients with rare diseases and unmet medical need, there is a clear demand from this side to limit the HE to situations where no alternative treatment is available by a centrally authorised ATMP. Similar critic is expressed by TiGenix (112), the MAH for ChondroCelect, which is the first ATMP to have successfully passed the centralised procedure at the EMA. Furthermore, Wilder (2012) of TiGenix concluded that the application of exempted products does not ensure the highest level of patient health protection as intended by the ATMP regulation (113). ChondroCelect is a TEP indicated for ACI. Although the central MA was obtained already in 2009, it took several years for successfully entering the EU market, which involved market acceptance and negotiations for reimbursement. In the meatime the product has been commercially launched in Belgium, Netherlands, Spain, the UK and Germany (76). As is shown in Table 3, there are other chondrocyte products now available in Germany under the HE, which,

according to Tigenix, represents unfair competition. Of note, the chondrocyte products available in Germany under the HE use slightly different technologies such as matrices as compared to ChondroCelect. If not allowed on the market in Germany under the HE, these potentially more advanced chondrocyte implantation technologies would not be available until the central MA is achieved.

Other contributions to the public consultation on ATMPs such as presented by the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE) view the HE as an important interim solution for ATMPs under development (46). The HE provides for the possibility to get the products reimbursed by the health insurance funds, which allows building up financial resources for bringing product development further towards the central MA. The HE has especially been important for products that had been on the markets of the MSs under national provisions before the ATMP regulation took effect in 2008. Taking Germany as an example, the majority of ATMPs that are now nationally authorised under the HE in Germany had already been on the market or used in the clinics (see Table 3). For most of these products CTs are ongoing and central MAAs are pending (as it is the case for co.don chondrosphere) or prepared. In these cases, the HE is not being used as a permanent option to circumvent the central MA but rather to build up the financial resources and product knowledge to eventually transition to the central MA. Especially for institutions developing ATMPs for rare diseases, the use of exempt ATMPs has been important to adequately design formal clinical studies (114). At least in Germany misuse of the HE is likely to be negligible, as continous reporting obligations to the PEI would identify those products which do no longer meet the eligibility criteria of the HE.

While the HE should not be used as a permanent alternative to the central MA for ATMPs that are commercialised on a larger scale, the HE may represent a long-term regulatory option for unauthorised ATMPs in non-commercial settings. Hospitals and academic institutions are unlikely to have the resources to ever obtain a central MA nor do they have the intention to market the products. However, some provide novel therapeutic approaches for a limited number of patients with rare diseases in which case the product development will unlikely to be feasable. For example, some surgical procedures using autologous cells from the bone marrow or adipose tissue for non-homologous at the Point of Care (PoC) in the operating theatre now fall under the ATMP regulation per definition, but such products are not intended to be ever placed on the market (115) (103). For these types of unauthorised ATMPs the HE could be a permanent regulatory option, ensuring the same quality level as for centrally authorised ATMPs and with equivalent provisions for pharmacovilance and traceability.

4.4 Relevance of the HE for patient´s access to unauthorised ATMPs

One of the aims of the ATMP regulations is to ensure the protection of human health by setting the same standards to the quality, safety and efficacy for ATMPs througout the EU. However, the ATMP field is differently structured than the traditional pharmaceutical industry for small molecules and far less dominated by big pharmaceutical companies. Development of ATMPs is generally science-driven and often arises from the results of fundamental research that needs to be translated from bench to bedside. Often intended for rare diseases with small patient populations, ATMPs seldom attract the commercial interest of big pharmaceutical companies (116). However, it is Big Pharma that would have the financial resources, manpower and expertise for the development of an ATMP towards a central MA. Hence, several ATMPs offering exciting new treatment options today would not have been available at all if there had not been enthusiastic individuals who were the driving forces behind it. On the one hand this means that the access to novel therapeutic approaches provided by unauthorised ATMPs still under development is of high value for patients without alternative treatment options available. On the other hand, this patient population is particularly vulnarable to false promises. Private clinics offering uauthorised stem cell therapies have raised the concern of the EMA over "stem cell tourism", meaning patients travel to countries were such treatments are permitted (117), but not fully evaluated for safety and efficacy. In Germany, the Company XCell-Center had been treating patients with stem cell preparations for intracerebral injections for several years under a manufacturing authorisation of the local competent authority without assessment of safety and efficacy (118). Due to the occurance of serious adverse reactions, the PEI classified the stem cell preparations as unsafe with the results that the company stopped this kind of treatments. Obviously, there needs to be a balance between the risks due to the limited knowledge available for unauthorised medicinal products and the potential benefits of the treatment.

According to Article 28 (2) of the ATMP regulation, also the HE is designed as a manufacturing authorisation following the implementation of national provisions in each MS. However, the european provisions of the HE do require the standards for the manufacturing and pharmacovigilance to be equivalent to centrally authorised ATMPs. Thus, treatments of patients with hospital-exempt ATMPs are provided under controlled conditions and hence the HE could be an important early access option for patients to innovative therapies. The risks to the patients depend largely on the national implementation of the HE, as the assessment of safety and efficacy of hospital-exempt ATMPs is not a requirement of Article 28 (2) of the ATMP regulation. As was shown in section 3.1, for Germany, a benefit/risk evaluation also of hospital-exempt ATMPs is performed (50), although the requirements are lower than for a central MA. Other MSs may accept supply of ATMPs under the HE only based on the quality of their manufacturing and also at very early stages of clinical development, as is the case in Finland (82). Also the expertise available for a profound assessment of ATMPs probably differs between the EU MSs. Such differences could potentially lead to very

different standards of ATMPs available under the HE throughout the EU and may compromise the access for patients to safe and efficous unauthorised ATMPs in certain MSs. One of the major achievements of the ATMP regulation was in fact the establishment of the CAT at the EMA, which centralizes the expertise for ATMPs available in EU in a multidisciplary teams to ensure the same standards for the assessment of ATMPs to be placed on the EU market (106).

The degree of evaluation may also have an effect on reimbursement and as a consequence also patient´s access to exempt ATMPs. According to the contribution to the public consultation on ATMPs by the CBG/MEB, "(…) the lack of a formalised Benefit/Risk assessment in the HE precludes reimbursement by Health Care Insurers in the Netherlands." (46). In Germany, reimbursement of hospital-exempt ATMPs by the statutory health insurance funds is feasible for example via the NUB-procedure (see section 3.1.3). However, there is no guarantee for the reimbursement for hospital-exempt AMTPs as this largly depends on successful negotiations

As shown in section 3.2, also eligibility criteria and the scope of the HE are differently construed in the EU MSs. While the Netherlands allow only max. of 10 patients to be treated with a hospital-exempt ATMP per year, other MSs such as Germany do not have numerical limits. Such limits on patient numbers raise ethical questions as to the availability of ATMPs. As the export and import of ATMPs supplied under the HE is prohibited, use of these ATMP is restricted to single MSs and therefore treatments are not available to patients in all MSs. As a result, patients from other MSs would have to travel to those MSs with certain hospital-exempt ATMPs available. Establishing such "ATMP tourism" should not be the aim, because the intention of the ATMP legislation was in fact to harmonise the market for ATMPs and to protect public health by establishing the same standards for ATMPs throughout the EU. Therefore, the overall aim should still be to make ATMPs available to all European patients by means of a central MA or maybe new approaches such as speciailised centres as suggested by the MEPs Against Cancer interest group at the European Parliament (119).

As a result of my investigations as part of this master thesis, a major issue is the lack of transparency on the availability of hospital-exempt ATMPs on the websites of NCAs apart of Germany. As shown in section 3.1.2, the online registry for ATMPs available under the HE provided for on the website of the PEI is an exemplary way to inform the public. As such patients can obtain information on the availability of therapies with hospital-exempt ATMPs. A central registry for ATMPs supplied under the HE in the EU MSs would increase the transparency on the availability of ATMPs under the HE.

For several years, products that now have to comply with the ATMP regulation were available to patients in the EU MSs under national provisions such as manufacturing licenses. Although in most cases the efficacy and safety of these products had not been assessed by controlled CTs, experience through the clinical applications supports the safe use of these products. The transitional period of Article 29 of the ATMP regulation allowed the continued supply of such existing ATMPs until the central MA became obligatory. However, most of the affected ATMPs did not obtain the central MA

so far. As a consequence marketing of these products was to stop by the end of the transitional period and several innovative treatments would not have been anymore available to patients. In Germany, submitting an application pursuant to Section 4b (3) AMG offered the opportunity to maintain marketing of existing ATMPs until the final decision on the HE. As is shown in Table 3, the first 4b authorisations were granted at the end of 2013, which in fact extended the transitional period defined by the ATMP regulation. Thus, the HE was and still is an important bridging tool for many existing ATMPs, not only for the companies to maintain marketing their products but also for patients to access existing therapies.

Notably, the HE is also a regulatory option for early access to newly developed unauthorised ATMPs as was shown for the tumour vaccine "DCVax-L" developed by NW Bio (see Table 3). In contrast to the ongoing Phase III CTs of "DCVax-L", the indication of "DCVax-L" under the HE is broader also including patients with different forms of Glioma. In this case, the HE offers the opportunity to make DCVax-L also accessible to patients who do not exactly fit the strict inclusion criteria of CTs. This may also be the case for the chondrocyte products currently available in Germany, both by centrally authorised ATMPs (ChondroCelect and MACI) and by means of the hospital-exempt ATMPs (e.g. Co.don chondrosphere). These products differ in the technologies used and some of the hospital-exempt products may be better suitable for bigger lesions of cartilage damages than centrally authorised ATMPs. In my opinion it is in the interest of patients to have access to different treatment opportunities and the HE offers such diversity by permitting locally supplied ATMPs. Also in the event that product availability is discontinued, as is currently the case for the centrally authorised chondrocyte product MACI after takeover of Genzmye by Sanofi (120), it is important to have treatment alternatives available.

As shown in section 3.3 there are other early access options available for patients to unauthorised ATMPs. Access to unauthorised ATMPs on a named patient basis according to Article 5 (1) of Directive 2001/83/EC appears to be only routinely applied in few MSs such as the UK (100). However, Article 5 (1) has not been implemented in all MSs and its application to ATMPs was one of the issues criticised during the public consultation on ATMPs (46). The other early access options to unauthorised ATMPs include CTs and CU programmes (see section 3.3). However, national provisions of CU programmes may not have been implemented in all EU MSs. While access to treatment within CTs depends on the fulfillment of inclusion criteria such as a narrow indication and also the availability of ongoing studies, CU programmes are restricted to life-threatening or serious debilitating diseases as well as advanced development of the product. In cases where an ATMP or a patient does not fit these criteria, ATMPs could still be available via the HE providing they fulfill the eligibility criteria. Importantly, Article 28 (2) of the ATMP regulation does not limit the HE to ATMPs to treatments in case of unmet medical need, although some of the contributions to the public consultation on ATMPs falsly claimed that this is already a requirement of the HE. Also, the German legal implementation of the HE into Section 4b AMG does not limit the exemption to certain disease

conditions or availability of alternative therapies. However, a justification of why patients cannot be treated with authorised medicinal products or other therapeutic therapies is in fact expected according to Module 5 of the HE dossier suggested by the PEI (44). It remains to be seen whether the expected legal revision of the ATMP regulation following the report from the European Commission to the European Parliament and the Council as of 28.03.2014 will amend the European provisions of the HE in this respect.

5 CONCLUSION AND OUTLOOK

The aims to establish an EU Regulation for ATMPs were to harmonize the european market for these products, ensure the protection of public health and foster innovation. However, the development of ATMPs is largely driven by SMEs, academia and hospitals, which have only limited resources and regulatory expertise to meet the requirements of a central MA as demanded by the ATMP regulation. The so-called HE, an exemption according to Article 28 (2) of the ATMP regulation from the obligation to obtain a central MA for ATMPs, which are prepared on a non-routine basis provided that the product is used for individual patients in a hospital under the professional responsibility of a medical practitioner, has turned out to be an important regulatory option, not only for already existing ATMPs that so far had been on the EU market under national provisons, but also for newly developed ATMPs. As Article 28 (2) of the ATMP regulation in fact amended Article 3 of Directive 2001/83/EC, the european provisions of the HE had to be implemented into the national laws of the EU MSs. As such the HE represents a nationally regulated exemption from the central MA with the european provisions of Article 28 (2) of the ATMP regulation being differently interpretated among the EU MSs. Moreover, guidances on the national procedures are scarce and information on the availability of hospital-exempted ATMPs is difficult to obtain with the exeption of few MSs.

In several MSs such as Germany, the HE is currently accepted as an interim solution to build up capital and clinical experience for the design of CTs and development towards the central MA. In addition, the HE is considered as a permanent refulatory option in other MS and also in Germany for specific cases. The HE has proven to be especially important for ATMPs that had already been clinically used in Germany before the ATMP regulation applied. In the absence of a central MA, such products would have disappeared from the market at the end of the transitional period set by the ATMP regulation. As a result of this many promising therapies provided by these unauthorised AMTPs would have not been available to patients any longer. As such the HE is an important option for patients to access unauthorised ATMPs under controlled conditions in addition to other early access options available to ATMPs including CTs, CU programmes and Named Patient Use.

Concerns over the HE as has recently been addressed in the public consultation on ATMPs. A major issue is the lack of harmonization of the eligibility criteria, which leads to a very heteregenous application of the HE to ATMPs in the different EU MSs. As a result, ATMPs could be accepted

under the HE in some MSs in order to circumvent the central MA und would represent unfair competition to centrally authorised ATMPs. Eventually, this could lead to a fragmented market of unauthorised ATMPs in the EU similar to the situation which existed when the ATMP regulation came into force in 2007. It appears to be a particular challenge to harmonize the market for ATMPs in the EU and at the same time not to compromise innovations and patient´s access to promising new treatments. Due to the nature of the ATMP field with limited resources and facing the multiple challenges of ATMP development, novel regulatory approaches towards the authorisation of ATMPs such as adaptive licensing, which is currently in the pilot phase at the EMA, are much needed. Following the report from the European Commission on ATMPs, a revision of the ATMP legislation including clarification of the conditions and requirements for the application of the HE is expected in the near future.

6 REFERENCES

1. European Parliament and the Council of the European Union. Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (consolidated version : 02.07.2012). *OJ L 324: 121-137, 10.12.2007. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2007_1394_cons_2012-07/reg_2007_1394_cons_2012-07_en.pdf (accessed 11.12.2014).

2. Jekerle, V., Schröder, C. und Pedone, E. Legal basis of the Advanced Therapie Regulation. *Bundesgesundheitsblatt.* 53: 4-8 (1020).

3. Sanzenbacher, R., et al. European regulation tackles tissue engineering. *Nature Biotechnology.* 25(10): 1089-1091 (2007).

4. European Commission. IPTS-JRC (Anne-Katrin Bock, Dolores Ibarreta, Emilio Rodriguez-Cerezo). Human tissue-engineered products: Today's markets and future prospects, Report EUR 21000 EN (2003). *European Commission, IPTS.* [Online] http://ec.europa.eu/health/files/advtherapies/docs/ipts21000en_en.pdf (accessed 10.12.2014).

5. Advanced therapies. *European Commission.* [Online] http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm (accesseed 10.12.2014).

6. Maciulaitis, R et al. Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive. *Molecular Therapy.* 20 (3): 479-482 (2012).

7. Commission, European. Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007: COM(2014) 188 final (Brussels, 28.03.2014). *European Commission.* [Online] http://ec.europa.eu/health/files/advtherapies/2014_atmp/atmp_en.pdf (accessed 10.12.2014).

8. European Parliament and the Council of the European Union. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (Consolidated version : 16/11/2012). *OJ L 311: 67-128, 28.11.2001. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf (accessed 11.12.2014).

9. Bundesministerium der Justiz und für Verbraucherschutz/juris GmbH. German Medicinal Products Act in the version published on 12 December 2005 (Federal Law Gazette [BGBl.]) Part I p. 3394, last amended by Article 1 of the Law of 19.10.2012 (Federal Law Gazette I p. 2192) (unofficial translation). *Arzneimittelgesetz in der Fassung der Bekanntmachung vom 12. Dezember 2005 (BGBl. I S. 3394), das zuletzt durch Artikel 2a des Gesetzes vom 27. März 2014 (BGBl. I S. 261) geändert worden ist. Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/englisch_amg/medicinal_products_act.pdf / http://www.gesetze-im-internet.de/bundesrecht/amg_1976/gesamt.pdf (10.12. 2014).

10. European Parliament and the Council of the European Union. Reg. (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. *OJ L136: 1-133, 30.04.2003. (Consolided version : 05/06/2013) European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (accessed 11.12.2104).

11. European Commission. Commission Directive 2003/63/EC of 25 June 2003 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use. . *OJ L159: 46-94, 27.06.2003. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_63/dir_2003_63_en.pdf (accessed 10.12.2014).

12. —. Commission Reg. (EC) No 668/2009 of 24 July 2009 implementing Regulation (EC) No 1394/2007 of the European Parliament and of the Council with regard to the evaluation and certification of quality and non-clinical data relating to ATMPs. *OJ, L 194: 7-10, 25.07. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2009_668/reg_2009_668_en.pdf (accessed 11.12.2014).

13. —. Commission Directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products. *OJ L 242: 3-12, 15.9.2009. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2009_120/dir_2009_120_en.pdf (accessed 11.12.2014).

14. Vol 4 EU guidelines for GMP, Annex 2 Manufacture of Biological active substances. *European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-4/vol4-an2__2012-06_en.pdf (15.09.2014).

15. Detailed guideline on good clinical practice to advanced therapy medicinal products (03.12.2009). *European Commission.* [Online] http://ec.europa.eu/health/files/eudralex/vol-10/2009_11_03_guideline.pdf (accessed 10.12.2014).

16. European Medicines Agency. Scientific guidelines for ATMPs. *European Medicines Agency Website.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp&mid=WC0b01ac05800862bd (accessed 10.12.2014).

17. Advanced therapies: Regulatory and procedural guidance. *European Medicines Agency.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000265.jsp&mid=WC0b01ac05800b378a (accessed 10.12.2014).

18. European Parliament and the Council of the European Union. Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells. *OJ L 102: 48-58, 7.4.2004. EUR-LEX.* [Online] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02004L0023-20090807&qid=1418338311195&from=EN (Accessed 11.12.2014).

19. —. Dir. 2002/98/EC of the European Parliamen and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC. *OJ L 33: 30-40, 08.02.2003. EUR-LEX.* [Online] . http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32002L0098&rid=3 (accessed 11.12.2014).

20. Council of the European Union. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices. OJ L 169: 1-43, 12.7.1993. *EUR-LEX.* [Online] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31993L0042&rid=5 (accessed 11.12.2014).

21. —. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices. OJ L 189: 17-36, 20.7.1990. *EUR-*

LEX. [Online] http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31990L0385&rid=3 (accessed 11.12.2014).

22. European Parliament and the Council of the European Union. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. *OJ L 378: 1-19, 27.12.2006. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf (accessed 11.12.2014).

23. European Parliament, Council of the European Union. Directive 2001/20/EC of the EP and of the C. of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the MS relating to the implementation of GCP in the conduct of CTs on medicinal products for human use. *OJ L 121: 34-44, 01.05.2001. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf (accessed 11.12.2014).

24. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use. *OJ L 348: 74-99 , 31.12.2010. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf (accessed 11.12.2014).

25. Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010. *OJ L 348: 1-16, 31.12.2010. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2010_1235/reg_2010_1235_en.pdf (accessed 11.12.2014).

26. Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use . *OJ L 262: 22-26, 14.10.2003. European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2003_94/dir_2003_94_en.pdf (accessed 11.12.2014).

27. Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 . *European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2011_62/dir_2011_62_en.pdf (accessed 11.12.20104).

28. Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products . *OJ L 334: 7-24, 12/12/2008. European Commission Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2008_1234/reg_2008_1234_en.pdf (accessed 11.12.2014).

29. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (consolidated version : 7/8/2009). *European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-1/reg_2000_141_cons-2009-07/reg_2000_141_cons-2009-07_en.pdf (accessed 11.12.2014).

30. Salmikangas, P. Challenges during development of ATMPs (CAT-DGTI Workshop,Dresden, 11.09.2014). *European Medicines Agency.* [Online] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/10/WC500176238.pdf (accessed 10.12.2014).

31. EMEA announcement to manufacturers, companies and hospitals having advanced therapy medicinal products legally on the Community market in accordance with national or Community

legislation (Doc. Ref. EMEA/326145/2008). *European Medicines Agency.* [Online] http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2009/10/WC500004073.pdf (11.09.2014).

32. Salmikangas, P. The Hospital Exemption for Advanced Therapies: the Regulator´s view (26th Annual EuroMeeting 25-27 March 2014, Vienna, Austria). *Epac presentation manager.* [Online] http://www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/36817.pdf (accessed 10.12.2014).

33. European Commission. Proposal for a regulation of the European Parliament and the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (16.11.2005). *European Commission.* [Online] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=COM:2005:0567:FIN:en:PDF (accessed 10.12.2014).

34. Kügel, J. W., Müller, R. und Hofmann, H. Arzneimittelgesetz: AMG Kommentar (1. Auflage). [Buchverf.] Pannenbecker. *§ 4b Sondervorschriften für Arzneimittel für neuartige Therapien.* s.l. : C.H. Beck, 2012, S. Rn. 1-39.

35. German Bundestag. Gesetz zur Änderung arzneimittelrechtlicher und anderer Vorschriften Vom 17. July 2009 / The 15th Amendment of the German Drug Act as of 17 July 2009. *Federal Law Gazette (BGBl.).* Part I Nr. 43, p. 1990 - 2020 (22.09.2009).

36. Paul-Ehrlich-Institut. Arzneimittel für neuartige Therapien Regulatorische Anforderungen und praktische Hinweise (as of June 2012). *Paul-Ehrlich-Institut, Innovation office.* [Online] http://www.pei.de/SharedDocs/Downloads/pu/innovationsbuero/broschuere-atmp-anforderungen-hinweise.pdf?__blob=publicationFile&v=1 (accessed 11.12.2014).

37. Dokumente ab 1949: Drucksache 16/12256 (16.03.2009). *Deutscher Bundestag.* [Online] http://dipbt.bundestag.de/dip21/btd/16/122/1612256.pdf (accessed 10.12.2014).

38. Bundesministerium der Justiz und für Verbraucherschutz / juris GmbH. German Transfusion Act / Transfusionsgesetz in der Fassung der Bekanntmachung vom 28. August 2007 (BGBl. I S. 2169), das durch Artikel 12 des Gesetzes vom 17. Juli 2009 (BGBl. I S. 1990) geändert worden ist. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/tfg/BJNR175200998.html (accessed 11.12.2014).

39. —. The Pharmacy Practice Order / Apothekenbetriebsordnung in der Fassung der Bekanntmachung vom 26. September 1995 (BGBl. I S. 1195), die zuletzt durch Artikel 1a der Verordnung vom 19. Februar 2013 (BGBl. I S. 312) geändert worden ist. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/apobetro_1987/ (10.12.2014).

40. Bakhschai, Bita. *Der Begriff des Inverkehrbringes im Arzneimittelgesetz.* [Hrsg.] J. Taupitz, H. Raspe und M. Oehlrich. Berlin : LIT Verlag, 2014. Bde. Medizin - Recht - Wirtschaft Band 11.

41. Dwenger, A., Straßburger, J. und Schwerdtfeger, W. Verordnung (EG) Nr. 1394/2007 über Arzneimittel für neuartige Therapien Umsetzung in innerstaatliches Recht. *Bundesgesundheitsblatt.* 53: 14-19 (2010).

42. PEI. The Innovation Office at the Paul-Ehrlich-Institut. *Paul Ehrlich Institut.* [Online] http://www.pei.de/EN/information/license-applicants/advice/innovation-office/innovation-office-atmp-node.html (accessed 30.11.2014).

43. Ziegele, B., Dahl, L. und Müller, A. T. Das Innovationsbüro am Paul-Ehrlich-Institut. *Bundesgesundheitsblatt.* 54: 857-866 (2011).

44. Genehmigung von nicht routinemäßig hergestellten ATMP nach. *Paul-Ehrlich-Institut.* [Online] http://www.pei.de/DE/infos/pu/genehmigungen/atmp-4b-amg/antraege-genehmigung-4b-amg-atmp-node.html;jsessionid=8DB8EFD221EE3C0996AE20A043BFFFE1.1_cid329 (accessed 30.11.2014).

45. Eudralex. Volume 2B Notice to Applicants Medicinal Product for human use: Presentation and format of the dossier Common Technical Document (CTD). *European Commission, Eudralex.* [Online] http://ec.europa.eu/health/files/eudralex/vol-2/b/update_200805/ctd_05-2008_en.pdf (accessed 30.11.2014).

46. European Commission. Public consultation on advanced therapy medicinal products. *European Commission.* [Online] http://ec.europa.eu/health/human-use/advanced-therapies/developments/2013_pc_atmp.htm (accessed 11.09.2014).

47. Erfahrungsbericht der Bundesregierung an den Bundesrat zum Gesetz zu Qualität und Sicherheit von menschlichen Geweben und Zellen (Gewebegesetz) Drucksache 688/09 (04.08.2009), page 30. *Bundesministerium für Gesundheit.* [Online] http://www.bmg.bund.de/fileadmin/dateien/Downloads/G/Gewebeprodukte/Erfahrungsbericht_der_Bundesregierung_an_den_Bundesrat_zum_Gesetz_ueber_Qualitaet_und_Sicherheit_von_menschen_Gewebe.pdf (accessed 10.12.2014).

48. German Transplantation Act / Transplantationsgesetz in der Fassung der Bekanntmachung vom 4. September 2007 (BGBl. I S. 2206), das zuletzt durch Artikel 5d des Gesetzes vom 15. Juli 2013 (BGBl. I S. 2423) geändert worden ist. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/tpg/gesamt.pdf (accessed 11.12.2014).

49. Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trial on medicinal products for human use / GCP-Verordnung - GCP-V). [Online] http://www.pei.de/SharedDocs/Downloads/EN/pu/clinical-trials/gcp-ordinance.pdf?__blob=publicationFile&v=1 (translation provided by the PEI) / http://www.gesetze-im-internet.de/bundesrecht/gcp-v/gesamt.pdf (accessed 28.11.2014).

50. Flory, E. und Reinhardt, J. European Regulatory Tools for Advances Therapy Medicinal Products. *Transfusion Medicine and Hemotherapy.* 40: 409-412 (2013).

51. Advanced Therapy Medicinal Products (ATMP). *Paul-Ehrlich-Institut.* [Online] http://www.pei.de/EN/medicinal-products/advanced-therapy-medicinal-products-atmp/advanced-therapy-medicinal-products-atmp-node.html (10.12.2014).

52. Agency, European Medicines. Human regulatory: Micro-, small- and medium-sized-enterprise (SME) register. *European Medicines Agency.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000483.jsp&mid=WC0b01ac05802a3166 (September 2014).

53. Buchholz, C., Sanzenbacher, R. und Schüle, S. The European Hospital Exemption Clause - New Option for Gene Therapy? *Human Gene Therapy.* 23:7-12 (2012).

54. Homepage. *co.don.* [Online] http://www.codon.de/home.html?L=1 (accessed 11.12.2014).

55. Homepage. *biotissue.* [Online] http://www.biotissue.de/ (accessed 11.12.2014).

56. Homepage. *TETEC.* [Online] http://www.tetec-ag.de/ (accessed 11.12.2014).

57. Sanzenbacher, R. FAQs and Answers: Quality and Preclinical Requirements for Approval of Cell-based Products (International Society for Cell Therapy, Belgirate, 14.09.2010). [Online] http://c.ymcdn.com/sites/www.celltherapysociety.org/resource/resmgr/uploads/files/Resources/EU%20LRA/Sanzenbacher%20ISCT%20Belgirate%202010-09handout.pdf (accessed 11.12.2014).

58. Clinical development . *UroTIss.* [Online] http://urotiss.com/en/product/clinical-development (accessed 11.12.2014).

59. Use of t2c001 in cardiac disease. *t2cure.* [Online] http://www.t2cure.de/pipeline/scientific_publications/use_of_t2c001_in_cardiac_disease/ (accessed 11.12.2014).

60. Official Section of the Federal Gazette. *Bundesanzeiger.* [Online] https://www.bundesanzeiger.de/ebanzwww/wexsservlet?global_data.language=en&session.sessionid=4745b5c24f76b043185c2fd4eedb22da&page.navid=gotolastpage (accessed 11.12.2014).

61. National Association of Statutory Health Insurance Funds. Statutory health insurance. *National Association of Statutory Health Insurance Funds / GKV-Spitzenverband.* [Online] http://www.gkv-spitzenverband.de/english/statutory_health_insurance/statutory_health_insurance.jsp (accessed 24.11.2014).

62. Book Five of the German Social Code / "Das Fünfte Buch Sozialgesetzbuch – Gesetzliche Krankenversicherung – (Artikel 1 des Gesetzes vom 20. Dezember 1988, BGBl. I S. 2477, 2482), das zuletzt durch Artikel 1 des Gesetzes vom 11. August 2014 (BGBl. I S. 134. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/sgb_5/ (accessed 24.11.2014).

63. (G-BA), The Federal Joint Committee. The Federal Joint Committee: Who we are and what we do. *The Federal Joint Committee (G-BA.* [Online] http://www.english.g-ba.de/structure/ (accessed 24.11.2014).

64. The Federal Joint Committee (G-BA). Rules of Procedure of the G-BA / Verfahrensordnung des Gemeinsamen Bundesausschusses, Version of 18.12.2008, last amended 19.06.2014. *The Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/richtlinien/42/ (accessed 24.11.2014).

65. Act on the Reform of the Market for Medicinal Products / Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (Arzneimittelmarktneuordnungsgesetz) vom 22. Dezember 2010. *German Federal Law Gazette.* part 1, 67: 2262-2277 (27.12.2010).

66. (G-Ba), The Federal Joint Committee. Nutzenbewertungsverfahren zum Wirkstoff Alipogentiparvovec. *The Federal Joint Committee (G-Ba).* [Online] https://www.g-ba.de/informationen/nutzenbewertung/146/ (accessed 25.11.2014).

67. The Federal Joint Committee (G-BA). Nutzenbewertungsverfahren zum Wirkstoff Sipuleucel-T. *The Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/nutzenbewertung/143/ (accessed 24.11.2014).

68. —. Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – matrixassoziierte autologe kultivierte Chondrozyten. *The Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/beschluesse/1739/ (accessed 24.11.2014).

69. —. Resolution inpatient methods / Richtlinie Methoden Krankenhausbehandlung: Autologe Chondrozytenimplantation (ACI) as of 22.05.2014. *The Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/beschluesse/1989/ (accessed 24.11.2014).

70. co.don. co.don® Aktiengesellschaft, Teltow Halbjahresbericht 2013 . *co.don AG.* [Online] http://www.codon.de/uploads/media/2013_codonAG_Halbjahresbericht_02.pdf (accessed 25.11.2014).

71. Directive Inpatient Methods / Richtlinie Methoden Krankenhausbehandlung, Version 21.03.2006, last amended on 19.06.2014. *The Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/richtlinien/34/ (accessed 24.11.2014).

72. Classifications, terminologies and standards in the health care system. *DIMDI.* [Online] https://www.dimdi.de/static/en/klassi/index.htm (accessed 25.11.2014).

73. Institut für das Entgeltsystem im Krankenhaus. Homepage. [Online] http://www.g-drg.de/cms/inek_site_de/layout/set/standard (accessed 25.11.2014).

74. Juris GmbH. German Hospital Fees Act / Krankenhausentgeltgesetz vom 23. April 2002 (BGBl. I S. 1412, 1422), das zuletzt durch Artikel 16d des Gesetzes vom 21. Juli 2014 (BGBl. I S. 1133) geändert worden ist. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/khentgg/BJNR142200002.html (accessed 25.11.2014).

75. Weber, S. White Paper - Erstattungsfähigkeit von innovativen Produkten der regenerativen Medizin und Advanced Therapy Medicinal Products (ATMP) durch die Gesetzliche Krankenversicherung (GKV) in Deutschland. *Cellogic GmbH.* [Online] http://www.cellogic.de/img/white_paper_zur_gkv_erstattung_von_innovationen.pdf (accessed 25.11.2014).

76. Tigenix Annual report 2013. *Tigenix.* [Online] http://www.tigenix.com/public/uploads/files/DOC%207%20-%20Annual%20report%202013_E.pdf (accessed 07.12.2014).

77. Geissler, A., et al. *Diagnosis-related groups in Europe (Chapter 14 Germany: Understanding G-DRGs, p. 243-271).* s.l. : Open University Press, 2011.

78. Northwest Biotherapeutics Press Release on 10.03.2014. *NW Bio.* [Online] http://www.nwbio.com/nw-bio-announces-two-german-approvals-hospital-exemption-for-early-access-program-with-dcvax-l-and-eligibility-of-dcvax-l-for-reimbursement/ (accessed 25.11.2014).

79. The Federal Joint Committee (G-BA). Testing examination and treatment methods in accordance with SGB V, section 137e. *The Federal Joint Committee (G-BA).* [Online] http://www.english.g-ba.de/special-topics/testing-regulations/ (accessed 25.11.2014).

80. European Commission. Pharmaceutical Committee - Meetings: PHARM608 Advanced Therapy Medicinal Products (ATMPs). *European Commission, Pharmaceutical Committee.* [Online] http://ec.europa.eu/health/files/committee/69meeting/pharm608_atmps.pdf (accessed 11.09.2014).

81. Austrian Medicines Products Act (AMG). *Jusline.* [Online] http://www.jusline.at/Arzneimittelgesetz_(AMG).html (accessed 11.12.2014).

82. Cuende, N., et al. The puzzling situation of hospital exemption for advanced therapy medicinal products in Europe and stakeholders´concerns. *Cytotherapy.* 0: 1-4 (2014).

83. Pellegrini, G. Limbal Stem Cell Therapy: From the Concept to a Product (The Product is the Process - Is it?, Berlin, 04.11.2014). [Online]

84. Danish Medicines Act. *Danish Health and Medicines Authority.* [Online] https://sundhedsstyrelsen.dk/en/medicines/safety/~/media/0C65F89DCCB74F9AAA0C24D28BED3B59.ashx (accessed 11.12.2014).

85. Inspectie voor de Gezondheidszorg (IZG). Geavanceerde therapie (ATMP): Procedure voor het verkrijgen van een hospital exemption voor ATMPs (versie april 2011). *Inspectie voor de Gezondheidszorg (IZG).* [Online]

http://www.igz.nl/Images/Procedure%20ATMP%20huisstijl%20rev%20april%202011_tcm294-283446.pdf (accessed on 14.11.2014).

86. sanitarios, Agencia Espanola de medicamentos y productos. Real Decreto 477/2014, de 13 de junio, por el que se regula la autorización de medicamentos de terapia avanzada de fabricación no industrial. *Terapias avanzadas.* [Online] http://www.boe.es/diario_boe/txt.php?id=BOE-A-2014-6277 (accessed on 14.11.2014).

87. Annex B - non-routine guidance. *MHRA.* [Online] http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con051880.pdf (accessed 11.12.2014).

88. MHRA. GUIDANCE ON THE UK'S ARRANGEMENTS UNDER THE HOSPITAL EXEMPTION SCHEME. *MHRA.* [Online] http://www.mhra.gov.uk/home/groups/es-policy/documents/publication/con065623.pdf (accessed 14.11.2014).

89. CAT: Agendas, minutes and reports (until September 2014). *European Medicines Agency.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000196.jsp#section1 (accessed September 2014).

90. European Medicinces Agency. Human medicines. *European Medicinces Agency.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124 (September 2014).

91. Co.don AG. News: Press release of 27.02.2013. *Co.don AG Website.* [Online] http://www.codon.de/news/einzelansicht/article/pressemitteilung-47.html?L=1 (accessed 11.09.2014).

92. Sarah O'Meara, Ph.D. Non-clinical Assessor. Hospital Exemptions: IMB policy and experience to date (PDA / IMB ESOF2012 Satellite Conference, Dublin 11.07.2012). *Irish Medicines Board.* [Online] https://www.hpra.ie/docs/default-source/default-document-library/6-sarah-o-39-meara.pdf (accessed 17.11.2014).

93. EU Clinical Trials Register. *https://www.clinicaltrialsregister.eu.* [Online] https://www.clinicaltrialsregister.eu/ctr-search/search (accessed 28.11.2014).

94. EU Clinical Trials Register. Clinical trials for DCVax-L. *EU Clinical Trials Register.* [Online] https://www.clinicaltrialsregister.eu/ctr-search/search?query=DCVAX-L (accessed 28.11.204).

95. Northwest Biotherapeutics Press release as of 14.10.2014. *NW Bio.* [Online] http://www.nwbio.com/dcvax-l-hospital-exemption-program-now-under-way-in-germany/ (accessed 28.11.2014).

96. Compassionate use. *European Medicines Agency.* [Online] http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000293.jsp (accessed 15.11.2014).

97. BfArM. Ordinance on Medicinal Products for Compassionate Use / Arzneimittel-Härtefall-Verordnung vom 14. Juli 2010 (BGBl. I S. 935) (AMHV). *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/amhv/gesamt.pdf (accessed 18.11.2014).

98. —. Leitfaden zur Anzeige eines Arzneimittel-Härtefallprogramms nach Arzneimittel-Härtefall-Verordnung (AMHV) Version 1.2 vom 25. März 2014. *BfArM.* [Online] http://www.bfarm.de/SharedDocs/Downloads/DE/Arzneimittel/Zulassung/klin-pr/compUse/BfArM-LeitfadenZuArzneimittel-

Haertefallprogrammen.pdf;jsessionid=2481801365A02ADF7BDA88A656D16480.1_cid350?__blob=publicationFile&v=2 (accessed 27.11.2014).

99. PEI. List of the Compassionate Use programmes of the Paul-Ehrlich Institut. *Paul-Ehrlich-Institut.* [Online] http://www.pei.de/EN/information/license-applicants/clinical-trial-authorisation/compassionate-use/list-of-programmes/list-of-programmes-node.html (accessed 15.11.2014).

100. MHRA. The supply of unlicensed medicinal products ("specials"), MHRA guidance note 14. *MHRA.* [Online] http://www.mhra.gov.uk/home/groups/is-lic/documents/publication/con413520.pdf (accessed 15.11.2014).

101. The Health Care Inspectorate (IGZ). Medicines without marketing authorization. *The Health Care Inspectorate (IGZ).* [Online] http://www.igz.nl/english/medicines/medicines_without_marketing_authorization/ (accessed 26.11.2014).

102. DGHO. Rechtliche Rahmenbedingungen der Einzeleinfuhr von Arzneimitteln nach Deutschland ("named patient use"). *Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie (DGHO).* [Online] https://www.dgho.de/informationen/stellungnahmen/lieferengpaesse/Rechtliche%20Rahmenbedingungen%20der%20Einzeleinfuhr%20von%20Arzneimitteln%20nach%20Deutschland.pdf/?searchterm=named%20patient (accessed 25.11.2014).

103. Schreiber, M. und Schäfer, M. Arzneimittel in der Erprobung Rechliche Betrachtungen zum individuellen Therapieversuch mit noch nicht zugelassenen Arzneimitteln. *Arzneimittel und Recht.* 3: 117-21 (2006).

104. Translation of the German Criminal Code provided by Prof. Dr. Michael Bohlander. Criminal Code in the version promulgated on 13 November 1998, Federal Law Gazette [Bundesgesetzblatt] I p. 3322, last amended by Article 3 of the Law of 2 October 2009, Federal Law Gazette I p. 3214. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/englisch_stgb/englisch_stgb.html#p0170 (accessed 18.11.2014).

105. PEI. Ordinance of Fee of the PEI / Kostenverordnung für Amtshandlungen des Paul-Ehrlich-Instituts nach dem Arzneimittelgesetz in der Fassung. *Bundesministeriums der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/pehrlinstkostv_1996/gesamt.pdf (accessed 06.12.2014).

106. The CAT and the CAT Scientific Secretariat. Challenges with advances therapy medicinal products and how to meet them. *Nature Reviews Drug Discovery.* 9: 195-201 (2010).

107. Salmikangas, P., et al. Regulatory requirements for clinical trial and marketing authorisation application for cell-bases medicinal products. *Bundesgesundheitsblatt.* 53: 24-29 (2009).

108. Britten, C. M., et al. The regulatory landscape for actively personalised cancer immunotherapies. *Nature Biotechnology.* 31(19): 880-882 (2013).

109. Närhi, M. und Nordström, K. Regulation of cell-based therapeutic products intended for human applications in the EU. *Regenerative Medicine.* 9(3): 327-351 (2014).

110. Ilona Reischl. The different facets of hospital exemption. *Regulatory Rapporteur.* 10: 11 (2013).

111. EudraGMDP database. *European Medicines Agency.* [Online] http://eudragmdp.ema.europa.eu/inspections/displayWelcome.do;jsessionid=d38kyN8oo-GADB4Io098as2MQWcfpto4DCj_QOgeQmtfA9js_-QK!-1559521869 (accessed 07.12.2014).

112. Bravo, E. The industry´s view. *Epac presentation manager.* [Online] http://www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/1035648.pdf (accessed 07.12.2014).

113. Van Wilder, P. Advanced Therapy Medicinal Products and Exemptions to the Regulation 1394/2007: How Confident Can We be? An Exploratory Analysis. *Frontiers in Pharmacology.* 3: 12 (2012).

114. Gaspar, H.B. und Swift, S. "Special Exemptions": Should They Be Put on Trial? *Molecular Therapy.* 21(2): 261-262 (2013).

115. Kleinherz, K. K. Autologous cell therapy manufactured in the hospital: ATMPs or not? (CAT-DGTI Workshop, Dresden, 11.09.2014). *European Medicines Agency.* [Online] http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2014/10/WC500176240.pdf (accessed 10.12.2014).

116. Kent, A.; Genetic Alliance UK. Hospital Exemption for ATMPs A Patient Perspective. [Online] http://www.epaccontrol.com/common/sitemedia/PrePost/PostPDFs/36892.pdf (accessed 09.12.2014).

117. CAT. Use of unregulated stem-cell based medicinal products. *The Lancet.* 376(9740): 514 (2010).

118. PEI. Stellungnahme des Paul-Ehrlich-Instituts zur intrazerbralen / intraventrikulären Anwendung von Stammzellpräparaten durch die Firma XCell-Center. *Landesärztekammer Hessen.* [Online] http://www.laekh.de/upload/Aktuelles/2010/aktuelles_2010_11_03_Stellungnahme_PEI.pdf (accessed 08.12.2014).

119. European Cancer Leagues. MEPs Against Cancer Round Table on ATMP (15.10.2013). *European Cancer Leagues.* [Online] http://www.europeancancerleagues.org/mac/mac-events/323-atmp15oct2013.html (accessed 09.12.2014).

120. EMA. MACI (matrix applied characterised autologous cultured chondrocytes) implant supply shortage (04.07.2014). *EMA.* [Online] http://www.ema.europa.eu/docs/en_GB/document_library/Supply_shortage/2014/07/WC500169589.pdf (accessed 08.12.2014).

121. Arzneimittel- und Wirkstoffherstellungsverordnung - AMWHV. *Bundesministerium der Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/amwhv/gesamt.pdf (accessed 11.12.2014).

122. German Law on Medical Devices / Medizinproduktegesetz in der Fassung der Bekanntmachung vom 7. August 2002 (BGBl. I S. 3146), das zuletzt durch Artikel 16 des Gesetzes vom 21. Juli 2014 (BGBl. I S. 1133) geändert worden ist. *Bundesministerium für Justiz und für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/mpg/gesamt.pdf (accessed 11.12.2014).

123. Ordinance on Tissues and Organs / TPG-Gewebeverordnung vom 26. März 2008 (BGBl. I S. 512), die zuletzt durch Artikel 1 der Verordnung vom 28. Mai 2014 (BGBl. I S. 600) geändert worden ist. *Bundesministerium der Justiz unnd für Verbraucherschutz.* [Online] http://www.gesetze-im-internet.de/bundesrecht/tpg-gewv/gesamt.pdf (accessed 11.12.2014).

124. Directive Inpatient Methods: autologous chondrocyte implantation / Richtlinie Methoden Krankenhausbehandlung: Autologe Chondrozytenimplantation (ACI). *Federal Joint Committee (G-BA).* [Online] https://www.g-ba.de/informationen/beschluesse/1989/ (accessed 25.11.2014).

125. Scherer, J., Seitz, R. und Cichutek, K. Wenn Ärzte "Arzneimittel" im OP oder am Krankenbett herstellen. *Deutsches Ärzteblatt.* 110(18): 872-876 (2013).

126. TiGenix Reports Full Year 2012 Financial Results. *Tigenix.* [Online] http://www.tigenix.com/public/uploads/files/DOC%2007%20-%20TiGenix_Registration%20Document%202013_ENG_FINAL.pdf (accessed 25.11.2014).

ANNEXES

Annex I: The legal framework applicable to ATMPs in the EU and Germany

Table 9: The legal framework applicable to ATMPs in the EU and Germany.

EU Law	Scope	Tranposition into law in DE
MEDICINAL PRODUCTS		
Regulation (EC) No 1394/2007 (1)	ATMPs	NA
Regulation (EC) No 726/2004 (10)	Centralised Procedure	NA
Directive 2001/83/EC -Annex I: Definition/Special Requirements Directive 2003/63/EC (11) Directive 2009/120/EC (13)	Community Code	AMG (9)
Regulation (EC) No 1901/2006 (22)	Paediatrics	NA
Directive 2001/20/EC (23)	Clinical Trials	German AMG and Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trial on medicinal products for human use (GCP-Verordnung - GCP-V) (49)
Directive 2010/84/EU (24) Regulation 1235/2010 (25)	Pharmacovigilance	AMG (9) NA
Directive 2003/94/EC (26)	GMP	Ordinance on the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients (Arzneimittel- und Wirkstoffherstellungsverordnung - AMWHV) (121)
Regulation (EC) No 141/2000 (29)	Orphans	NA
Regulation (EC) 1234/2008 (28)	Variations	NA
Directive 2011/62/EU (27)	Falsified Medicine	AMG (9)
MEDICAL DEVICES		
Directive 93/42/EEC (20) Directive 90/385/EEC (21)	Medical Devices Active Implantable Medical Devices	*Law on Medical Devices (Medizinproduktegesetz - MPG*) (122)

BLOOD		
Directive 2002/98/EC (19)	Human blood and blood components	German Transfusion Act (*Transfusionsgesetz - TFG*) (38)
TISSUE / CELLS		
Directive 2004/23/EC (18)	Human tissues and cells	German Transplantation Act (48) (*Transplantationsgesetz - TPG*) Ordinance on Tissues and Organs *(TPG-Gewebeverordnung - TPG GewV*) (123)

NA = not applicable.

Annex II: Legal definitions of ATMPs according to Article 2 of Regulation (EC) No 1394/2007 and part I of Annex I of Directive 2001/83/EC

Article 2 of Regulation (EC) No 1394/2007 (1)

Definitions

1. In addition to the definitions laid down in Article 1 of Directive 2001/83/EC and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC, the following definitions shall apply for the purposes of this Regulation:

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

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

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

— a tissue engineered product as defined in point (b).

(b) 'Tissue engineered product' means a product that:

— contains or consists of engineered cells or tissues, and

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

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

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

(c) Cells or tissues shall be considered 'engineered' if they fulfil at least one of the following conditions:

— the cells or tissues have been subject to substantial manipulation, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

(d) 'Combined advanced therapy medicinal product' means an advanced therapy medicinal product that fulfils the following conditions:

— it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and

— its cellular or tissue part must contain viable cells or tissues, or

— its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

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.

4. A product which may fall within the definition of a tissue engineered product and within the definition of a somatic cell therapy medicinal product shall be considered as a tissue engineered product.

5. A product which may fall within the definition of:

— a somatic cell therapy medicinal product or a tissue engineered product, and

— a gene therapy medicinal product,

shall be considered as a gene therapy medicinal product.

Part IV, Annex I of Directive 2001/83/EC (8)

(…)

2. DEFINITIONS

For the purposes of this Annex, in addition to the definitions laid down in Regulation (EC) No 1394/2007, the definitions set out in sections 2.1 and 2.2 shall apply.

2.1. Gene therapy medicinal product

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

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

(b) its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

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

2.2. Somatic cell therapy medicinal product

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

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

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

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

Annex III: Section 21a (1-8) of the German Medicinal Products Act (AMG) (9)

Section 21a
Authorisation of tissue preparations

(1)Tissue preparations which are not manufactured involving an industrial process and the essential processing procedures of which are sufficiently well known in the European Union, and the effects and adverse reactions of which are known and evident from scientific data may only be placed on the market within the purview of the present Act, if they have been authorised by the competent higher federal authority, by way of derogation from the marketing authorisation obligations pursuant to Section 21 sub-section 1. This shall also apply to tissue preparations the processing procedures for which are new but comparable with a known procedure. Sentence 1 shall apply *mutatis mutandis* to blood stem cell preparations intended for autologous use or for targeted administration to a specific person. The authorisation shall cover the procedures for the procurement, processing and testing, the choice of donors and the documentation for each operational step as well as the quantitative and qualitative criteria for tissue preparations. Especially the critical processing procedure must be evaluated to ascertain that the procedures do not render the tissues clinically ineffective or harmful to patients.

(1a) An authorisation pursuant to sub-section 1 is not required for tissue preparations which are intended for clinical trials on human beings.

(2) The application for an authorisation shall be accompanied by the following information and documents to be supplied by the applicant:

1. the name or the company and the address of the processor,

2. the name of the tissue preparation,

3. the therapeutic indications as well as the method of administration and, in the case of tissue preparations which are intended to be used for a limited period of time, the duration of the application,

4. information about the procurement and laboratory testing of the tissues, as well as the processing, preservation, testing and storage of the tissue preparation,

5. the type of preservation, the shelf life, and the conditions for storage,

6. a description of the functionality and the risks of the tissue preparation,

7. documents containing the results of microbiological, chemical and physical examinations and the methods used in their determination, in so far as these documents are necessary, as well as

8. all of the information and documents which is relevant to the purpose of evaluation of the medicinal product.

Section 22 sub-section 4 shall apply *mutatis mutandis*.

(3) In respect of the information pursuant to sub-section 2 number 3, scientific findings which are also able to compare with empirical medical findings prepared according to scientific methods can be submitted. These could include studies conducted by the manufacturer of the tissue preparation, data from publications or subsequent assessments of the clinical findings on the manufactured tissue preparations.

(4) The competent higher federal authority shall reach a decision on the application for an authorisation within five months. If the applicant is given the opportunity to correct flaws, the deadlines shall be interrupted until such flaws have been corrected or until the expiry of the deadline set for the correction of the flaws. The interruption of the deadline shall begin on the day the applicant receives the request to correct the flaws.

(5) The competent higher federal authority shall grant the authorisation in writing, together with an authorisation number. The authority may combine the authorisation with the imposition of conditions. Section 28 and section 34 shall apply *mutatis mutandis*.

(6) The competent higher federal authority may only refuse an authorisation if:

1. the documents submitted are incomplete,

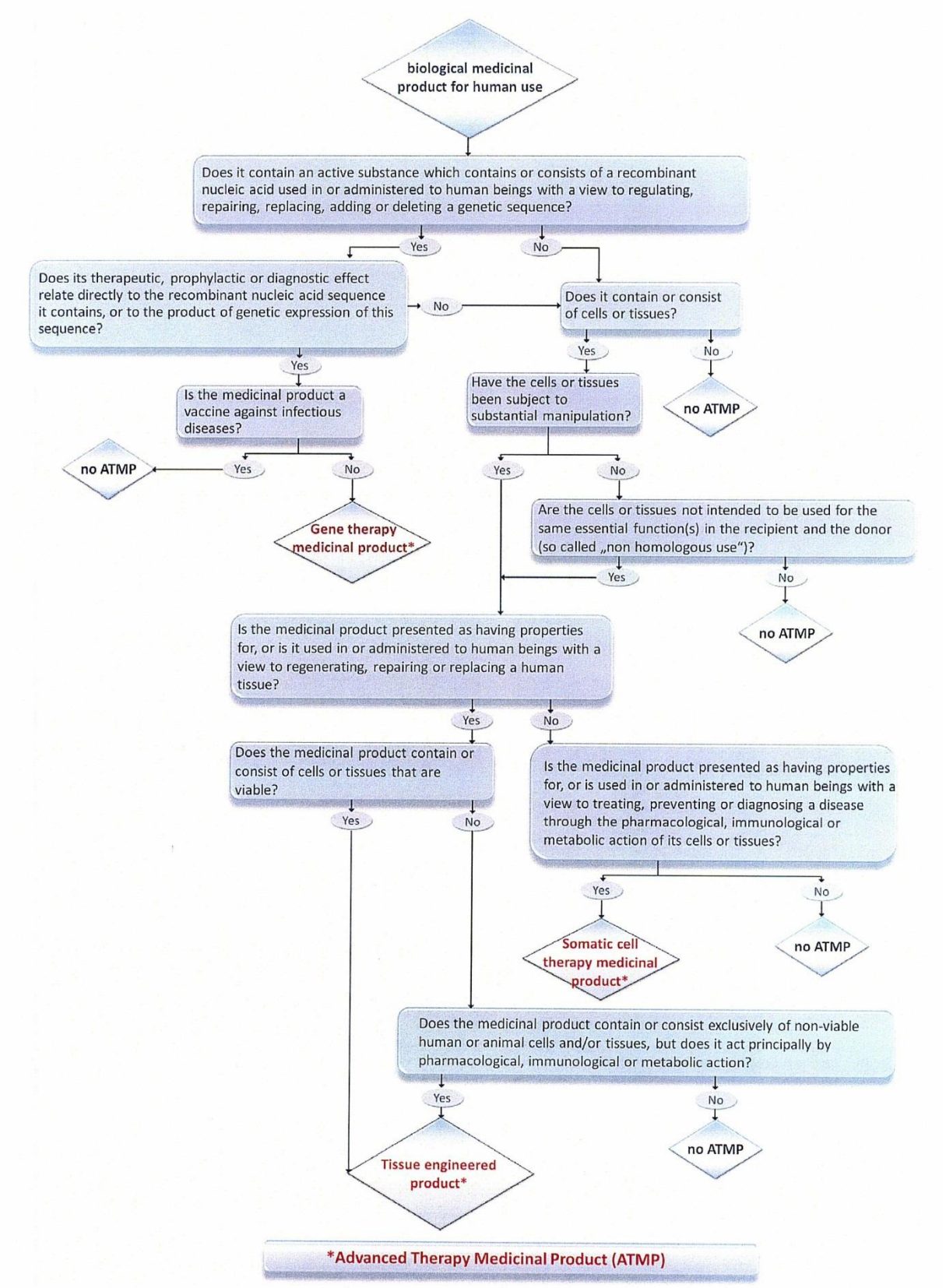
2. the tissue preparation does not correspond to the current state of scientific knowledge, or

3. the tissue preparation does not fulfil the envisaged function or the risk-benefit balance is unfavourable.

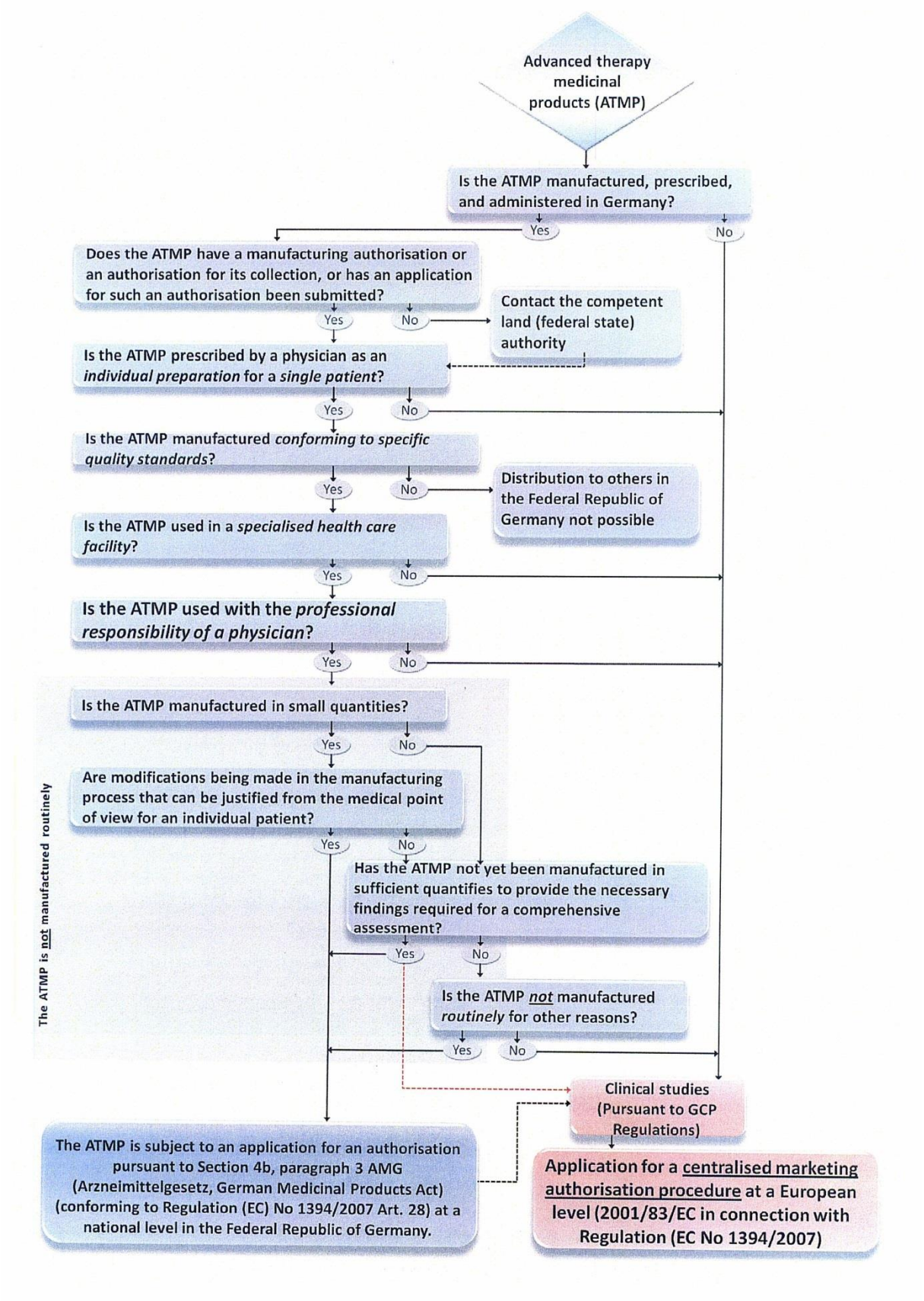
(7) The applicant, or subsequent to the authorisation, the holder of the authorisation shall immediately notify the competent higher federal authority of any changes in the information pursuant to sub-sections 2 and 3 and include the corresponding documents with the notification. In the event of a change in the documents pursuant to sub-section 3, the change may only be carried out if the competent higher federal authority has consented.

(8) The authorisation shall be withdrawn if it subsequently becomes known that one of the grounds for refusal, pursuant to sub-section 6 numbers 2 and 3 existed at the time the authorisation was granted. The authorisation shall be revoked if one of the grounds for refusal subsequently developed. In both cases, the temporary suspension of the authorisation may also be ordered. Before a decision is reached pursuant to sentences 1 to 3, the holder of the authorisation shall be heard unless danger is imminent. If the authorisation has been withdrawn, revoked or suspended, the tissue preparation may not be placed on the market, nor shall it be introduced into the purview of the present Act.

Annex IV: Decision Tree for Classification of Medicinal Products as ATMPs (40)



Annex V: Decision Tree for Section 4b AMG (German Medicinal Product Act) (40)



Annex VI: Suggested forms and templates for applications for an authorisation pursuant to Section 4b, 3 AMG (German Medicinal Products Act) (42)

The current versions of the Modules 0, 1, 3A, 3B, 4 and 5 published on the PEI website as of 09.12.2014 are provided on a CD attached to this master thesis.

Module 0: Classification of the medicinal product and eligibility check

Qualification as an ATMP, ATMP classification (GTMP, TEP, sCTMP), check of eligibilty criteria for the HE.

Module 1: Description of the medicinal product / administrative information

Application form: Information on the ATMP: name and active substances, qualitative and quantitative composition, manufacturing, procurement, adminstrative data on non-clinical and clinical studies, local QPPV (*Stufenplanbeauftragter*), manufacturing sites, information on the hospitals, the qualification of the doctor.

Product information: SmPC, labelling and package leaflet.

Information on the expert (*Sachverständigen):* Quality, non-clinical, clinical.

Safety system for the ATMP: pharmacivigilance system, risk-management plan, safety specifications regarding preclinic and clinic, safety and efficacy follow-up, additional pharmacovigilance activities, risk-minimisation activities.

Environmental risk evaluation in case of Gene Manipulated Organisms (GMOs).

Module 3A: Quality data for sCTMPs, TEPs and GTMPs

Information on the active substance:

General information: nomenclature, structure, general properties of the active substance.

Manufacturing: manufacturer, manufacturing process, control of materials, controls of critical manufacturing steps and intermediates, process validation, manufacturing process development.

Characterisation: elucidation of structure and other characteristics; impurities.

Control of active substance: specifications, analytical procedures, validation of analytical procedures, batch analyses, justification of specifications, reference standards or materials, container and container closure system.

Stability.

Information on the medicinal product

Description and composition of the medicinal product.

Pharmaceutical Development.

Manufacturing: manufacturer, pharmaceutical development, description of manufacturing and process controls, control of critical steps and intermediates.

Control of excipients: specifications, analytical procedures, validation of analytical procedures, justification of specifications, excipients of human or animal origin, novel excipients.

Control of Drug Product: specifications, analytical procedures, validation of analytical procedures, batch analyses, characterisation of impurities, justification of specifications.

Reference Standards or Materials.

Container and container closure system.

Stability.

Appendices: Facilities and Equipment, Adventitious Agents Safety Evaluation; Regional Information with information on medical devices.

Module 3B: Quality data for stem cell preparations from bone marrow or peripheral blood that are non-substantially manipulated but that are for non-homologous use

Composition of the stem cell product: composition of active substances; composition of ek excipients; pack size.

Starting materials: informaton donor; container; list of medical devices; other starting materials.

Manufacturing procedures: Flow chart; List of equipment; list of materials (antibodies, solutions etc.)

Testing procedures: control of starting materials; control of fnished product; quality characteristics; testing of kryopreserved preparations; measures to avoid potential infections;

Quality and stability: description of methods; composition and conclusion of quality and stabilit.

Other information, literature; References.

Module 4: Non-clinical data - Pharmacodynamic, Pharmacokinetic, Toxicology

Non-clinical data: pharmacodynamic, pharmakokinetic, toxicology.

Literature and references: summary tables of non-clinical studies.

Note: Although the standard non-clinical programme may not be applicable for many ATMPs, information on non-clinical studies in relevant animal models for pharmacodynamic, pharmacokinetics and toxicology should be provided. Toxicology studies need to conform to GLP. In addition to own non-clinical studies, it is also possible to support the data with relevant published data. Lack of data needs to be scientifically justified. The non-clinical studies and other relevant publications have to be presented as tables.

Module 5: Clinical data -Clinical Information on Efficacy and Safety of the ATMP, Benefit-Risk-Analysis

Clinical information on efficacy and safety of the ATMP

Risk-benefit analysis

Literature and references

Appendices: clinical study reports

Note: If own clinical studies are missing, the clinical information for the ATMP may be supplied by other medical data such as publications or re-examination of clinical findings. Lack of clinical data is possible but it needs to be further explained in the respective sections.

The existing clinical data has to be presented as summaries and detailed presentation of all relevant clinical studies. The clinical data can be supported also with results from observational studies and other available information on efficacy and safety of the medicinal product.

Of note, it has to be justified that no alternative treatment or authoried medicinal products are available.

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

Bonn, 12. Dezember 2014

Dr. Anna Schnitger