biopharma excellence by PHARMALEX

Study on Hospital Exemption for ATMPs in Selected EU Countries – FINAL REPORT

For the Federal Office of Public Health (FOPH) / BUNDESAMT FÜR GESUNDHEIT (BAG), BERN, SWITZERLAND

PharmaLex GmbH
Harrlachweg 6
68163 Mannheim
Germany

Contact:
Dr. Zaklina Buljovcic
Director, Principal Consultant
Phone No. +49 621 181538-0
E-Mail: Zaklina.buljovcic@pharmalex.com

January, 2022

INHALTSVERZEICHNIS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ABM	Agence de la biomédecine (French; Biomedicines Agency)
ADR	Adverse Drug Reaction
AEMPS	Spanish Agency for Medicines and Health Products
AG	Aktiengesellschaft (German; Public limited Company)
ALL	Acute Lymphoblastic Leukaemia
AMG	Arzneimittelgesetz (German; Medicines Act)
AMNOG	Arzneimittelmarktneuordnungsgesetz (German; Medicines Market Reorganisation Act)
ANSM	Agence Nationale de sécurité du médicament et des produits de santé (French; National Agency for the Safety of Medicines and Health Products)
AP-HP	Assistance Publique des Hôpitaux de Paris (French; Public Hospitals of Paris)
AT	Austria
ATIMP	Advanced Therapy Investigational Medicinal Products
ATMP	Advanced Therapy Medicinal Product
BASG	Bundesamt für Sicherheit im Gesundheitswesen (Austrian Federal Office for Safety in Health Care
BSG	Blutsicherheitsgesetz (German; Blood Safety Act)
BVL	Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (German; Federal Office of Consumer Protection and Food Safety)
CAR-T cell	Chimeric Antigen Receptor T cell
CAT	Committee for Advanced Therapies
CH	Switzerland
CHMP	Committee for Medicinal Products for Human Use
CIK-cells	Cytokine-activated Killer Cells
CIT	Cancer Immunotherapy
CMO	Commercial Manufacturing Organisations
CMV	Cytomegalovirus
CP	Centralised Procedure
CSP	Code de la Santé Publique (French; Public Health Code)
CTD	Common Technical Document
DC	Dendritic Cell
DE	Germany
DIS/DIC	Donor Identification Sequence/Code
eAF	Electronic Application Form
EAMS	Early Access Medicine Scheme
EC	European Commission
EEA	European Economic Area
EFS	Établissement français du sang (French Blood Establishment)
EMA	European Medicines Agency
ES	Spain
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
EVWEB	EudraVigilance website

FDA	Food and Drug Administration
FR	France
G-BA	Gemeinsamer Bundesausschuss (German; Federal Joint Committee)
GBM	Glioblastoma Multiforme
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
GSG	Gewebesicherheitsgesetz (German; Tissue Safety Act)
GTG	Gentechnikgesetz (German; Genetic Engineering Act)
GTMP	Gene Therapy Medicinal Product
GvHD	Graft-versus-Host-Disease
HE	Hospital Exemption
HMRs	Human Medicines Regulations
HSCT	Hematopoietic stem-cell transplantation
HTA	Human Tissue Authority
IB	Investigational Brochure
ICH	International Council for Harmonisation
ICP	Immune Checkpoint Inhibitor
ICRS	International Cartilage Regeneration & Joint Preservation Society
ICSR	Individual Case Safety Report
IGOR	Institut für Gewebe- und Organkonstruktion (German: Institute for Tissue and Organ Reconstruction)
IMPD	Investigational Medicinal Product Dossier
IGJ	Inspectie Gezondheidszorg en Jeugd (Dutch; Health Care and Youth Inspectorate)
LT	Lithuania
LVFS	Läkemedelsverkets föreskrifter (The Medical Products Agency Regulation)
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MACI	Autologous Cultured Chondrocytes on Porcine Collagen Membrane
MeAT	Manufacturers License exempt Advanced Therapy Medicinal Products
MHRA	Medicines and Healthcare Products Regulatory Agency
MMD	Medicines and Medical Devices
MS	Member State
MSC	Mesenchymal stem cells
MTI PP	Médicaments de Thérapie Innovante Préparés Ponctuellement (French; Punctually Prepared Innovative Therapy Medicines)
NB	Notified Body
NC1	Autologous bone marrow-derived mesenchymal stem cells
NEES	Non-eCTD Electronic Submission
NHL	Non-Hodgkin's Lymphoma
NL	The Netherlands
OOS	Out of Specification
PEI	Paul-Ehrlich Institute
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PIM	Promising Innovative Medicine

PIP	Paediatric Investigation Plan
PL	Poland
PSMF	Pharmacovigilance System Master File
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QP	Qualified Person
QPPV	Qualified Person of Pharmacovigilance
RA	Risk Assessment
RAEFAR	AEMPS Registry database
RMP	Risk Management Plan
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SCTMPs	Somatic Cell Therapy Medicinal Products
SE	Sweden
SEC	Single European Code
SmPC	Summary of Product Characteristics
TEP	Tissue-engineered Product
TFG	Transfusionsgesetz (German; Transfusion Law)
TPG	Transplantationsgesetz (German; Transplantation Act)
TPG GewV	Transplantationsgesetz Gewebeverordnung (German; Transplantation Act Tissue Ordinance)
UK	United Kingdom

1 Executive Summary

In the European Union (EU), the Advanced Therapy Medicinal Product Regulation (EC) 1394/2007 was implemented on 30 December 2008 including a mandatory Centralised Marketing Authorisation for ATMPs. §28 (2) of the regulation is laying out the requirements to allow the use of Advanced Therapy (ATMPs, short "advanced therapies"), under certain circumstances, in individual EU member states. This so called "Hospital Exemption (HE)" enables non-routine manufacturing and administration of advanced therapies *"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"*, i.e. to a usually small number of patients in the respective Member states already early in clinical development.

In this report, six countries (DE, FR, NL, ES and SE, as well as UK) have been chosen and their implementation of the HE into practice has been analysed in detail.

All countries apply adapted GMP for ATMPs case-by-case, as well as common EU Pharmacovigilance (PV) and Traceability rules. Most countries apply the definition of "non-routine" on a case-by-case basis per product. As of writing of this report, the overall number of authorized HE products was below 10 per country. Some EU countries appear not not to apply the HE concept at all.

In all cases, specific documentation must be provided; for some countries the data required is elaborate and even CTD-like structuring of submissions may be required. Emphasis is put on the pharmaceutical quality of the product. Even if clinical data are sometimes not mandatory, a positive benefit-risk assessment is required in all cases.

Only two countries (Germany and Spain) provide product names and an approved Summary of Product Characteristics (SmPC) for their HE products on their webpages.

Im- and export is not favoured under the HE scheme, likely because the Regulation stipulates that such products are *"used within the same Member State"*. UK uses the "Specials" scheme which enables im- and export. France adapted their laws in a way that at least theoretically appears to allow im- and export in exempted cases.

The administration of gene therapies under HE was only approved in Spain. In France, it is possible to use them in the context of clinical trials.

A comprehensive summary of rules, use and examples of HE for the countries analysed for this report is provided. This report provides recommendations on what to consider for a de-novo hospital exemption provision in a given legislation. Most importantly, mechanisms are recommended to control products authorised by HE, e.g., provision of annual reports by hospital exemption holders; a limited duration of its authorisation subject to extension by the authority; a requirement for HE holders to apply for any changes made and approval of such by the authority; and the possibility for the authority to withdraw an authorisation granted.

The main goal should always be to provide a reasonably safe, promising, innovative and possibly life-saving option to a patient who would otherwise not have this option, balanced against the need to get systematic data on quality, safety and efficacy and not to circumvent or counteract regular authorisation routes and/or clinical trial execution.

2 Introduction

Advanced therapy medicinal products (ATMPs, short "advanced therapies") comprise a complex class of biologic medicinal products, including gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (SCTMPs), tissue-engineered products (TEPs) as well as combined ATMPs (where an ATMP is combined with a medical device where this device is integral part of the product). While gene therapy medicinal products and somatic cell therapy medicinal products had already been legally defined in the EU via Annex I of Directive 2001/83/EC, a legal definition of tissue-engineered products was then provided with the ATMP Regulation (EC) 1394/2007.

Following the implementation of the ATMP Regulation (EC) 1394/2007 on 30 December 2008, it became mandatory for ATMPs to follow the centralised procedure to obtain a marketing authorisation pursuant to Regulation (EC) No. 726/2004. Consequently, ATMPs had to fulfil the same high regulatory standards as other pharmaceuticals, including manufacturing in compliance with Good Manufacturing Practice (GMP), pivotal clinical trials establishing their benefits and risks, and paediatric investigation plans (PIPs). These requirements have put a significant regulatory burden on ATMP developers and manufacturers who are often small biotechnology companies (mostly small and medium-sized enterprises, SMEs) and academic institutions, but also established a clear regulatory framework in order to obtain sufficient data on quality, safety and efficacy to support licensure.

However, an exemption from the centralised procedure was introduced to the ATMP Regulation to allow the use of ATMPs, under certain circumstances, in individual EU member states (MS), the so-called "Hospital Exemption" (HE). According to this exemption, EU MS are allowed to permit the use of ATMPs in their respective territories without the need for a centralised marketing authorisation (MA).

Based on §28 (2) of the Regulation, the Hospital exemption can only be applied to any advanced therapy medicinal product:

- which is prepared on a non-routine basis according to specific quality standards,
- used within the same Member State (MS) 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.

Therefore, the Hospital exemption can only be applied for specific circumstances for custom-made ATMPs used in a hospital setting for a specific patient. Such products are produced under the

responsibility of a physician (and not the manufacturer or a Marketing Authorisation Holder as with authorized medicines), and are only to be used within the member state where it is manufactured.

However, there are requirements: second indent of §28, a competent authority must authorise the hospital exemption for a given product, and it must comply with the equivalent requirements concerning pharmaceutical quality, traceability and pharmacovigilance that apply to centrally authorised ATMP medicinal products.

3 Problem statement and scope

As a default, in the EU all ATMPs require a central Marketing Authorization (MA). However, the Hospital exemption clause was included into the ATMP Regulation because ATMPs can provide new and innovative treatments and, in some cases, even healing options to very ill patients while they sometimes can be difficult to manufacture on a routine or industrial basis. Via this route a legal option exists for products where a centralised approval is not feasible but where access to such treatment to individual patients should be enabled provided that quality and safety are not undermined.

The EU legislators left it up to the MS how to implement the HE clause in their respective countries and therefore transferred the paragraph to the Directive 2001/83/EC for implementation into national law. Therefore, while basic requirements were defined (see in chapter above), the HE was implemented in different ways throughout the MS, which resulted, for example, in differences regarding requirements for pharmaceutical quality, or the amount and format of data to be submitted to the National Competent Authority for granting a HE. In some MS, HE approvals are issued as a specific manufacturing license, while in other MS the manufacturing license is a prerequisite for HE approval but further non-clinical, and possibly clinical data, are requested to enable a benefit-risk analysis prior to approval.

Further, there was no EU-wide definition provided for “non-routine” preparation, and if and when repeated manufacture would transition into “routine”, or even “industrial manufacture”

The ATMP Regulation lays out that the same rules for traceability and pharmacovigilance apply for the HE as for the centralised MA. Though this is applied by the MS, differences arise in the details of how reporting is expected, the format of reports and required data.

The ATMP Regulation defines the overall quality and manufacturing standard required, which is GMP, for ATMPs. The basic GMP requirements are the same throughout the EU.

Behind this background, the Swiss Federal Office of Public Health (FOPH; Bundesamt fuer Gesundheit, BAG) requested an overview of how HE has been implemented in several representative EU MS countries:

- What kind of products are authorised under HE in individual countries?
- Which regulations, e.g. GMP regulations, do applicants have to comply with?
- What kind of facilities fall under the definition of a “hospital”?
- How is the term "non-routine" defined in the different countries?

This report provides an overview of the implementation of the HE in several EU countries (and UK) in order to provide a basis for FOPH for an own decision-making process.

In detail, the report was requested to include:

1. A selection of EU countries to be considered (in addition to DE, FR and UK) with justification on their choice.
2. A summary of the respective national legal and regulatory frameworks (including relevant guidance) (if any).
3. An overview of the total number of products per selected country and per category, where possible.
4. Concrete examples of HE products where possible (with justification of selection), with reference to the GMP standards the manufacturer had to comply with.
5. Presentation of challenges or difficulties that these products may present and solutions proposed or already implemented where possible.
6. How these products are monitored for pharmacovigilance and proof of efficacy, if available (e.g., with registries).
7. A summary of the results and discussion with recommendations.

4 Approach

Required information per country was defined in a standardised manner and researched on the respective competent national authority's website and in available literature.

Apart from an initial shortlist of EU countries requested by BAG (DE, FR and UK), further EU countries have been selected (NL, ES and SE), based on publicly available information.

Justification for selection is provided in the single chapters. Overall, reasons for choosing further countries could be detailed information available, representative information, interesting solutions etc.

Every country chapter follows the same structure.

5 Results

5.1 Germany

Germany was the first country to translate §28 of the regulation into German Medicinal Products Law ("Arzneimittelgesetz", AMG) in 2009 with the 15th Amendment (Novelle) of the AMG.

The National Authority responsible for granting a hospital exemption is the Paul-Ehrlich Institute (PEI). Manufacturing and tissue establishment licenses are granted by local authorities ("Länderbehörden").

5.1.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

For ATMPs, as for all drugs, clinical trials form the basis for a later marketing authorisation. Clinical trials are designed to systematically collect valid scientific data on the efficacy and/or safety of a drug and this data is part of the later MAA.

After the introduction of the Hospital Exemption ("§4b Approval" or "Krankenhausausnahme-genehmigung") into the AMG, hospitals and companies had an additional pathway, parallel to the clinical studies route, to provide innovative medicine at an early development stage to patients. Figure 1 below shows the two pathways; clinical trial and the "4b Approval" including the requirements for the HE Approval.

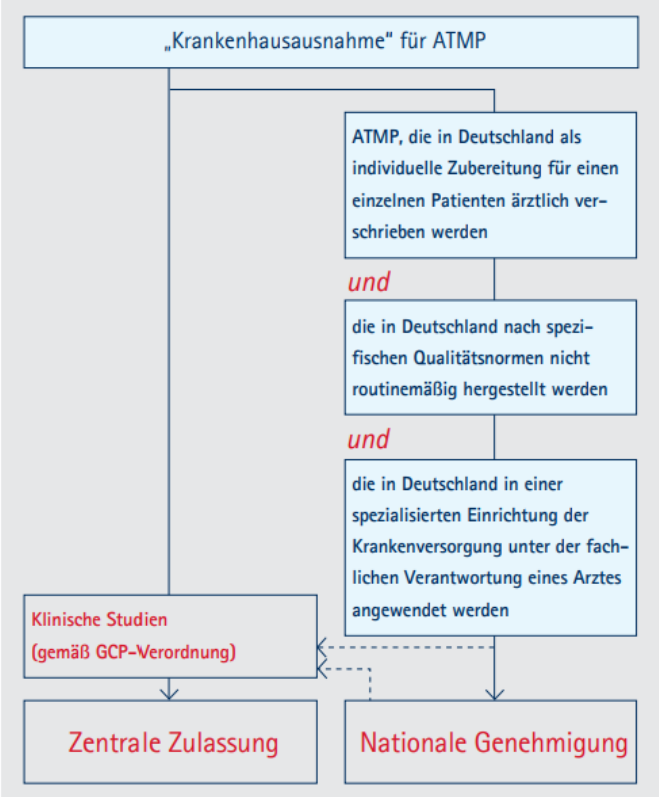

Figure 1: Scheme for the two pathways; clinical studies and §4b exemption. From PEI Info Brochure.

The "Hospital Exemption" is translated into the AMG and specified in §4b.:

Definition §4b (1)

"Für Arzneimittel für neuartige Therapien, die im Geltungsbereich dieses Gesetzes

1. als individuelle Zubereitung für einen einzelnen Patienten ärztlich verschrieben (*custom-made & individual medical prescription*),
2. nach spezifischen Qualitätsnormen nicht routinemäßig hergestellt (*according to specific quality standards non-routinely manufactured*) und
3. in einer spezialisierten Einrichtung der Krankenversorgung unter der fachlichen Verantwortung eines Arztes angewendet (*administered in a specialised facility for patient-care under the professional responsibility of a medical practitioner*)".

All steps (i.e., prescription, production and administration of the product) have to take place in Germany.

Note that in the German Legislation *"used within the same Member State (MS) in a hospital"* was translated as "applied in a specialized healthcare institution". This opens more possibilities for application and manufacturing as compared to only hospitals. This means that companies and commercial manufacturing organisations (CMO) and hospitals can manufacture the product provided that they have the appropriate GMP facilities. Generally, either a hospital or a company can apply for a HE. Administration to the patient can take place in hospitals (stationary or ambulatory) or medical practices (ambulatory) depending on the ATMP and indication.

Definition of non-routine

The definition of "non-routine" is provided in §4b (2) AMG:

"…

1. die in so geringem Umfang hergestellt und angewendet werden, dass nicht zu erwarten ist, dass hinreichend klinische Erfahrung gesammelt werden kann, um das Arzneimittel umfassend bewerten zu können, (*which are manufactured and used on such a small scale that it is not to be expected that sufficient clinical experience can be gained to fully evaluate the medicinal product, or*), oder *(or)*
2. die noch nicht in ausreichender Anzahl hergestellt und angewendet worden sind, so dass die notwendigen Erkenntnisse für ihre umfassende Bewertung noch nicht erlangt werden konnten." (*which have not yet been produced and applied in sufficient numbers so that the necessary knowledge for their comprehensive evaluation has not yet been obtained*).

Point 1 includes products which are manufactured on a small scale by hospitals for a very small number of patients without a commercial sponsor and where it is not expected that products will ever achieve a central MA. This should not stop sponsors from conducting clinical studies to gain scientific knowledge in a controlled setting.

Point 2 addresses applicants that are developing a product, but who do not have enough evidence for a central Marketing Authorisation yet. In this context the HE is a kind of early access to patients who are not part of clinical trials. Therefore, the indication for the product might differ (slightly) between the clinical trials and the HE.

No number of products is defined that would define when "non-routine" becomes "routine". It is decided on a case-by-case basis depending on the product and indication, the development status and the risk-benefit analysis.

An overview of the §4b decision process is shown in

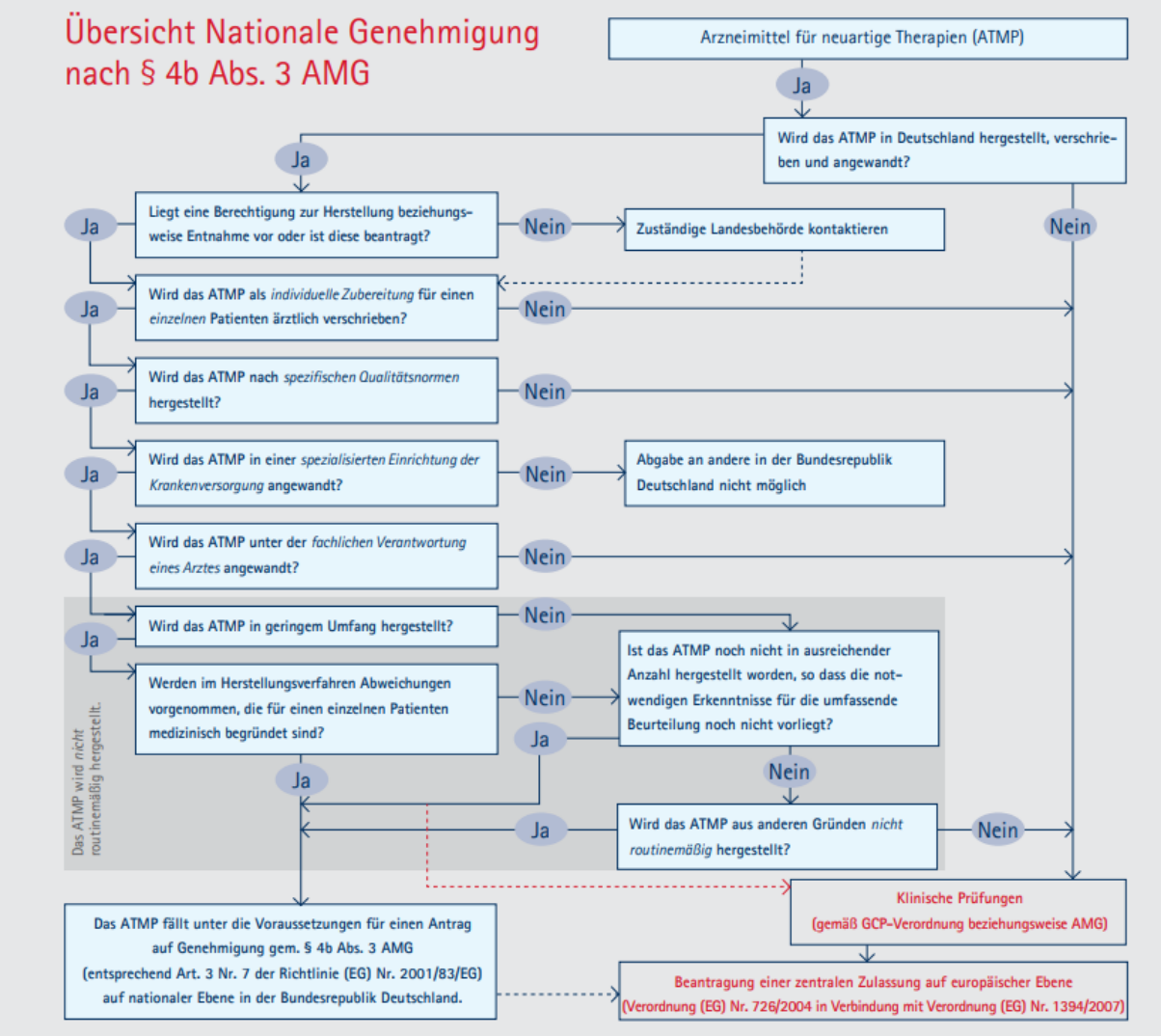

Figure 2.

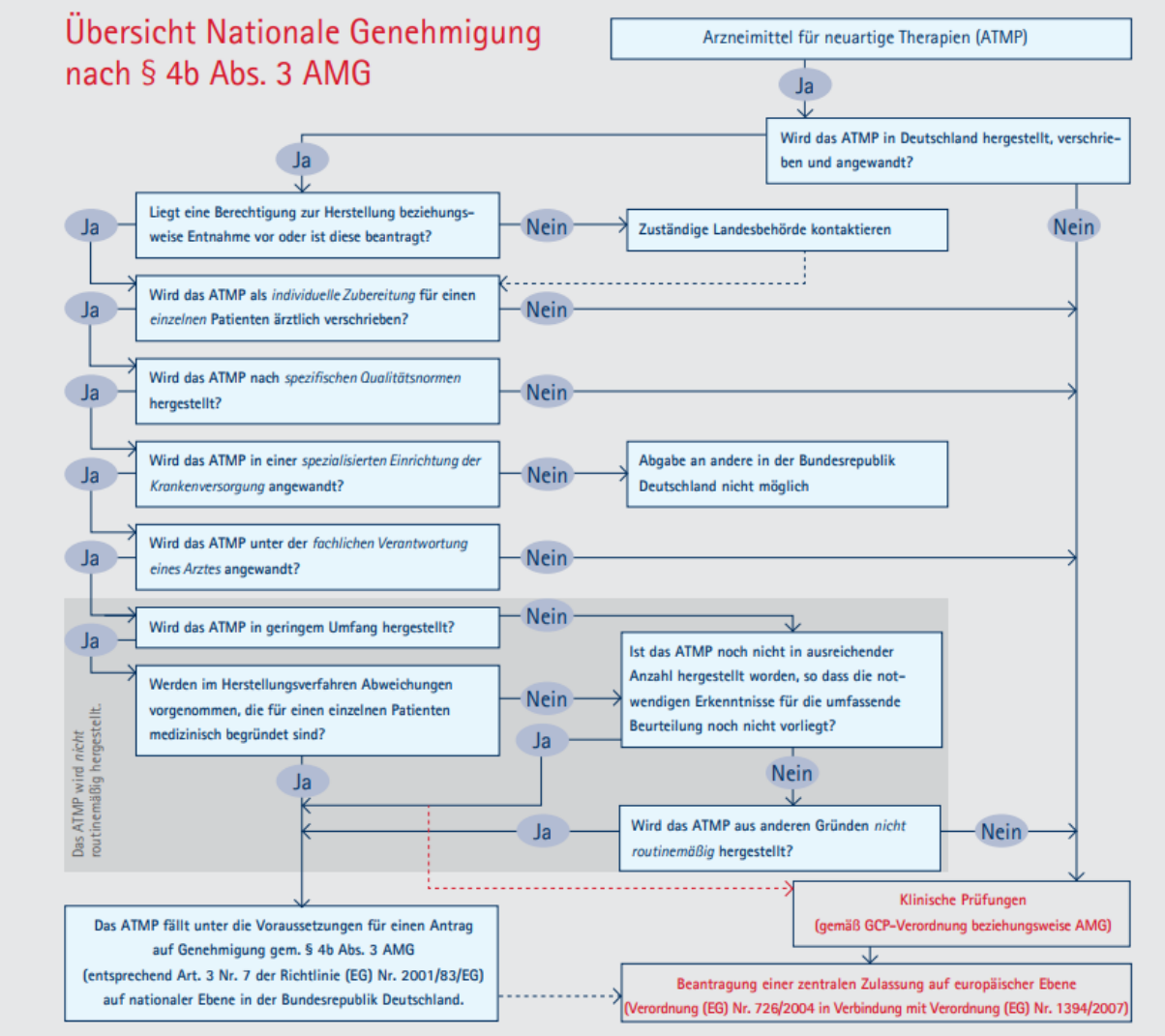

Figure 2: Overview on §4b Decision process. From: PEI Innovationsbüro, Info Brochure

Meaning of specific quality standards

As nationally approved ATMPs must meet the same specific quality standards that apply at European level to centrally authorised ATMPs, production must take place according to GMP. Therefore, facilities need to hold a manufacturing license according to §13 AMG and manufacture under GMP. The relevant overarching applicable GMP guidance is "GMP for ATMPs".

A manufacturing license can be issued to a hospital or to a commercial manufacturing organisation (CMO).

Manufacturing or preparation of the product can, but does not have to, take place at the clinic. The product can be shipped to the specialised facility for patient care within Germany.

Documentation required

The required documentation is addressed in §4b (3) AMG. A CTD-like dossier needs to be prepared. This includes Modules 1 to 5 (Module 2 without summaries). Module 1 includes the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL), Labelling information, Pharmacovigilance (PV)-System, Risk Management Plan (RMP) and Environmental Risk Assessment for Genetically Modified Organisms (RA for GMOs). The relevant Forms are provided on the PEI homepage.

The applicable fee for an HE procedure ranges from 4,250 to 17,000 EUR (Section 2b of the "Kostenverordnung Paul-Ehrlich-Institut").

Licenses required

The Hospital Exemption Approval ("Krankenhausausnahmegenehmigung") according to §4b (3) AMG, (therefore also called "§4b-Genehmigung") is granted by PEI. This approval is required when the product is to be dispensed to other parties before actual treatment of a patient takes place. Dispensing to others, within the meaning of §4 (17) AMG, occurs when the actual power of disposal over a medicinal product changes.

The power of disposal ("Verfügungsgewalt") refers to the authorisation of disposal ("Verfügungsberechtigung"). The decisive factor for the assessment of who is responsible for disposal is the organisation of the manufacture and use of a medicinal product and the form of the authorisation granted by the competent authority. Practically this means when one manufacturer or one hospital is manufacturing the product but it is administered at another hospital (or even in another department of the same hospital). For further discussion refer to Chapter 5.1.4.

Regardless, for the manufacturing of an ATMP a manufacturing license according to §13 AMG (which includes manufacturing according to GMP) is required.

Further procurement licenses are required for tissue and blood-derived starting materials, based on the tissue and blood directives: Tissue establishment licenses (§§20b or 20c AMG) and manufacturing license (§13 AMG) for blood. These licenses are based on the respective EU Directives (Directive 2004/23/EC for tissues and 2002/98/EC for blood).

5.1.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

§4b (1) AMG sets out that §14 (Pharmacovigilance) and §15 (Traceability) of the regulation (EC) 1394/2007 need also to be applied.

Pharmacovigilance

In detail, it is required that the §4b-Approval holder establishes a PV-System based on a Quality Management System.

Reporting is required for ATMPs as well as for cells, tissues or blood used as starting materials and which are part of donations. Three Forms address serious adverse reactions at recipient or donor site as well as reactions due to manufacturing or distribution.

Further, a periodic annual report is required (§4b (7)). This is usually requested in form of a PSUR (periodic safety report), although specific adaptations are possible (e.g. number of produced products; respectively number of treated patients)

Finally, a RMP (risk management plan) is also required as part of the §4b application dossier.

Traceability

The sponsor/manufacturer has to establish a system for traceability (including a specific batch numbering system) for the ATMP, which also allows tracing back to the starting material. Traceability for ATMPs follows the rules set down in the "GMP for ATMPs" guidance: Chapter 6.6:

"6.35 A system that enables the bidirectional tracking of cells/tissues contained in ATMPs from the point of donation, through manufacturing, to the delivery of the finished product to the recipient should be created."

For the traceability of cells and tissues used as starting materials for ATMPs, the European "SEC" code applies (AMG §4 (30a)) and follows the rules set by Directive 2006/86/EC and for blood by 2002/98/EC.

In detail for starting materials, the following apply:

- Cells and tissues: §13c (Rückverfolgbarkeit) of the TPG (Transplantationsgesetz) and the TPG GewV (TPG Gewebeverordnung) apply
- For blood: the TFG (Transfusionsgesetz) applies

5.1.3 PRODUCTS APPROVED UNDER A HOSPITAL EXEMPTION SCHEME

Overview and History

After the transition period of the ATMP regulation for TEPs (30 December 2012), companies who already had products (in Germany mostly TEPs) legally on the market, based on a manufacturing license, would lose their licenses.

Before closing of this transition period PEI announced a timeline during which an application form for a §4b-Approval had to be provided, and subsequently a dossier was required. As long as the decision had not been made, companies were still allowed to market their products.

Nonetheless, some companies announced they would stop ATMP development.

All approved products (either centrally or under §4b) including the respective SmPCs are accessible on the PEI webpage.

Most §4b applications (approximately seven) were approved in 2013 and 2014; three were submitted and approved later. As of writing of this report, there were seven TEP and two SCTMP approvals, respectively.

However, in the past years very few new applications were approved. It is not known how many applications were made that were rejected. A few renewals took place around 2018; however, there was only one new approval, in 2021 (Amesanar, allogeneic ABCB5-positive mesenchymal stroma cells).

On the other hand, some companies did not renew their approvals, e.g., DCVax-L, a dendritic cell product (SCTMP) to treat Glioblastoma multiforme (GBM). In general, voluntary non-renewal of a HE could be for various reasons, for example:

- The Company/hospital might want to stop the program;
- The Company is preparing for centralised MAA;
- The PEI did not accept the renewal.

Examples

Three examples are provided:

1. co.don chondrosphere® (TEP)
2. Obnitix (TEP)
3. Cytokine-activated Killer cells (CIK-cells) (SCTMP)

No gene therapy medicinal products have been approved.

1. Co.don chondrosphere® (TEP)

Description:	co.don chondrosphere, 10-70 Sphäroide/cm^2 matrixassoziierte Zellen zur Implantation, Suspension zur Implantation
Indication:	„Behandlung von isolierten akuten und chronischen symptomatischen Gelenkknorpelschäden der Tibia des Knies, an der Hüfte, an der Schulter, am Sprunggelenk und am Ellenbogen bei Erwachsenen. Für Jugendliche mit geschlossener Wachstumsfuge in dem betroffenen Gelenk ist das Arzneimittel indiziert für die Behandlung von isolierten akuten und chronischen symptomatischen Gelenkknorpelschäden am Knie, an der Hüfte, an der Schulter, am Sprunggelenk und am Ellenbogen.“
Why chosen:	This product is an example for a number of different chondrocyte products on the German market.
Challenges:	After co.don AG received the centralised MA of Spherox®, the §4b indication of co.don chondrosphere (same product) was adapted and no longer covered the indication of the centrally authorised product. This means that the treatment of the femural condyle of the knee and the patella are excluded in the HE. However, the product is still available for

	the treatment of other joints. See the indications below and in the SmPC Co.don chondrosphere (see on PEI website) (co.don 2019).
Indication Spherox (CP):	Repair of symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Regeneration & Joint Preservation Society [ICRS] grade III or IV) with defect sizes up to 10 cm^2 in adults and adolescents with closed epiphyseal growth plate in the affected joint.
Indication Chondrosphere (§4b): (femural condyle of knee and patella is excluded)	Treatment of isolated acute and chronic symptomatic articular cartilage damage of the knee tibia, hip, shoulder, ankle and elbow in adults. For adolescents with closed growth plate in the affected joint, the product is indicated for the treatment of isolated acute and chronic symptomatic articular damage of the knee, hip, shoulder, ankle and elbow. co.don chondrosphere® can be used up to a defect size of 10 cm^2 (grade III or IV according to the criteria of the International Cartilage Regeneration & Joint Preservation Society [ICRS]). When treating defects with a size of more than 10 cm^2 a consultation with the manufacturer is required beforehand.

2. Obnitix (TEP)

Description:	humane allogene mesenchymale Stromazellen, expandiert (TEP), Suspension zur intravenösen Infusion
Indication:	"Obnitix wird zusätzlich zur konventionellen Therapie mit Immunsuppressiva (Cyclosporin A, Prednisolon u.a.) zur Behandlung einer steroidrefraktären, akuten Graft-versus-Host-Disease (GvHD) Reaktion (Grad II – IV) von Patienten nach allogener Stammzelltransplantation angewendet."
Why chosen:	This is a TEP in an Orphan Indication which is not very common. N.B.: It might be disputable whether this TEP should rather be classified as a SCTMP instead of a TEP.
Challenges:	Obnitix has been in clinical use since 2012 and approved under §4b in 2016. According to the SmPC (medac 2020) (can be viewed also at the PEI website) the §4b approval is partly based on non-clinical studies, publications and case studies. Efficacy seems to have been based on a retrospective data analysis of 92 patients. Furthermore, 38 aGVHD patients have been treated in the period 2017-2018 and an additional 21 patients case studies have been provided post-approval. The product has been developed by the Institute of Transfusion Medicine and Immunohematology and German Red Cross Blood Center

Frankfurt am Main and sold to the Company medac who started a multicentre Phase III trial.

3. Zytokin-aktivierte Killerzellen (CIK-Zellen), allogen, (SCTMP)

Description:	$1x10^8$ $CD3^+CD56^-$ T-Zellen/kg Körpergewicht in 100 ml Infusionsdispersion
Indication:	„Zytokin-aktivierte Killerzellen (CIK-Zellen) werden angewendet zur Behandlung von Leukämiepatienten mit molekularem Rezidiv nach allogener Stammzelltransplantation.“
Why chosen:	For a long time this product was the only approved SCTMP (after DCVax-L was not renewed based on the Company' decision).
Challenges:	It is not known if this product will ever be developed for the market. This can be seen as a representative of §4b (2) No 1 approval. According to the SmPC (DRK BaWüHe 2014) (which can be also viewed at the PEI website) it was approved in 2014 based on 9 treated patients (Bonig et al. 2019). No randomised / controlled studies have been performed. The German Red Cross Blood Center Baden-Württemberg - Hessen GmbH holds the approval.

Specific indications or products excluded?

No indications or product types are excluded *per se*. Products which are developed for Orphan indications can be approved for a longer time period (e.g. 5 years compared to the usual 3 years) before renewal of the HE approval. Note that a yearly PSUR is always required.

At the time of writing of this report, no gene therapies have been approved under §4b which is probably due to their different risk profiles. However, they are not explicitly excluded: §4b (4) stipulates that the approval of GMOs has to take place in conjunction with the Federal Office of Consumer Protection and Food Safety (Bundesamt fuer Verbraucherschutz und Lebensmittelsicherheit, BVL) which is responsible for approval of GMOs in Germany. ERA is required (Annex II, III and IV of Directive 2001/18/EC) establishing that unacceptable harmful effects on the health of third parties and on the environment are not to be expected.

5.1.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

Duration of the procedure

The PEI needs to provide a decision on an §4b-Approval within 5 months. The entire duration of the procedure also depends on the clock-stops during which applicants need to answer questions put by the authority and provide more details. Therefore, based on experience, it can take about a year to receive an approval. This will also depend on the indication and the medical need, and may be shorter currently.

Co-existence of HE and centralised approval for the same product

One issue with the Hospital exemption, not restricted to Germany, is that there can be a competition between HE products and centrally approved products with the same or a similar indication on the national market, in this example the German market. “non-routine” manufacturing when there are, at the same time, also authorised products of a similar kind via the EU Centralised Procedure.

In Germany, chondrocyte products are administered via chondrocyte implantation and are considered a “method” via the G-BA (Federal Joint Committee). In this case the treatment is the generally recognized state of medical knowledge and accepted by the vast majority of the relevant experts (physicians, scientists) to support the treatment method and there is, therefore, a consensus on the appropriateness of the therapy. A reimbursement in the hospital is usually possible. For more details refer to Gaissmaier et al 2018. For products that are considered “products” in the stricter sense, not “methods” (not TEPs), an application according to the AMNOG procedure (“Arzneimittelmarktneuordnungsgesetz“, German Medicines Market Reorganisation Act) is required. §4b products however do not apply for AMNOG up to now. For a more detailed discussion on reimbursement we would like to refer to the upcoming specific reimbursement section.

Clinical evidence base

Usually for initial §4b-approval, the PEI would take into consideration initial existing clinical data (such as a Phase I or I/II trial), however that would also depend on the risk-benefit and risk-profile. For example, for the Cytokine activated killer cell (CIK) product data from only nine patients were sufficient for an initial application.

“Dispensing to other parties”

Under German law an approval according to §4b (3) AMG is required when the product is dispensed to other parties (“Abgabe an Andere”), see general description in Chapter 5.1.1. This means that in a case where the head of department of a health care facility (hospital) is directly responsible for the manufacture of the ATMP (the same for other medicinal products) in their department and also uses it in their department, this is NOT considered to be a “dispense to others”, and an authorisation in accordance with § 4b paragraph 3 AMG is NOT required in this case. The same is true when other doctors use it under the supervision of the head of the department.

A manufacturing authorisation (including GMP) according to § 13 Para. 1 AMG is required for ATMPs that are administered by a doctor (or another person authorised to practice medicine) under their direct professional responsibility for the purpose of their administration to a specific patient.

However, also in case of ATMPs which do not have to be approved or authorised according to §4b or §21 AMG certain requirements apply: § 63j AMG “Dokumentations- und Meldepflichten der behandelnden Person für nicht zulassungs- oder genehmigungspflichtige Arzneimittel für neuartige Therapien” apply as well as the need for a manufacturing authorisation. Both are under the responsibility of the local Authority (“Landesbehörde”).

Due to this law, it is possible that hospitals that produce and administer ATMPs within their own departments can do so without the need for a HE (because they do not "dispense" in a legal sense). In these cases, PEI cannot monitor these products.

In such cases it is possible that patients can also receive individually locally prepared products that are dedicated own products while centrally authorised products may also exist see web article).

5.1.5 SUMMARY

- The HE, also called "§4b-Approval", is issued by the PEI.
- Approval according to §4b (3) AMG is required when the product is disposed to other parties ("Abgabe an Andere"). If no disposal takes place (e.g. in the same department of a hospital) only the manufacturing license is required.
- The HE approval according to §4b (3) AMG is based on a CTD dossier like structure, including clinical evidence and a manufacturing license.
- There is a significant effort (costs and resources) to prepare the §4b Dossier.
- A graduate plan officer ("Stufenplanbeauftragter": similar to QPPV), a PV-System and QP (GMP) is required.
- 4b-Approval can take up to one year (including clock-stops).
- An approval is usually restricted in duration (3-5 years).
- The approval can be modified and renewed.
- An annual report is required.
- The PEI provides a transparent database of all §4b products and access to SmPCs.
- Products that received a centralised MA may compete with §4b approvals in the same or similar treatment areas (a general finding with HE, not just in Germany).
- The §4b is still "in use" even if at a much lower extent than during the first years after the Regulations' transition period.
- Currently 10 products are approved.
- Reimbursement might be applicable and differs depending on if the product is considered a product or a method used in the hospital.

5.2 France

The initial authorisation, as well as modification, authorisation or renewal of the authorisation of an establishment or organisation is issued by the Director General of the ANSM (Agence Nationale de sécurité du médicament et des produits de santé).

The MTI PP (médicaments de thérapie innovante préparés ponctuellement) is the French adaptation of "hospital exemption product".

5.2.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

The French version of the Hospital exemption definition is addressed in the Public Health Code (Code de la santé publique, CSP).

The law dated 22/03/2011 article L.5121-1 CSP Number 17 (Loi du 22/03/2011 art L.5121-1 du CSP au 17°) defines the Hospital exemption product as:

An advanced therapy medicinal product:

- prepared on an ad hoc basis ("Médicament de thérapie innovante préparé ponctuellement"; MTI-PP), any medicinal product as defined in 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,
- manufactured in France,
- in accordance with specific quality standards and
- used in a hospital in France,
- under the responsibility of a doctor,
- to carry out a specific medical prescription for a product specially designed for a specific patient.

These medicinal products are subject to authorisation by the ANSM. The authorisation may be subject to special conditions or restrictions of use. By way of derogation, these medicinal products may also be manufactured, imported or exported as part of the research defined in Article L. 1121-1 of the CSP. The authorisation may be modified, suspended or withdrawn.

The Agence de la biomédecine (ABM) is informed of the decisions taken in application of article 17 and is responsible for the scientific assessment of the application, providing their opinion to ANSM. The ABM is responsible for transplantation and tissues in France, so they provide for advice to the ANSM for cell-based products. The ABM is also in charge of biovigilance (see chapter 5.2.2).

ANSM will grant the authorisation based on the ABM's opinion. The authorisation procedure takes 90 days after receiving the complete dossier (Bonnaud-Vrignaud et al. 2015).

In France, this has resulted in the possibility to produce ATMPs on a small scale, for local use and on the basis of a prescription by name of medicines that meet the definition of MTI (MTI-PP, corresponding to the original intention of the EC). These are manufactured not by a pharmaceutical establishment, but by a hospital pharmaceutical establishment, by a hospital or blood establishment (Établissement français du sang, EFS) infrastructure or any other institution, whose premises and work organisation comply with good pharmaceutical manufacturing practices.

Definition of non-routine

There is no specified limit or definition. The French law uses the expression "prepared on an ad hoc basis" ("préparé ponctuellement") instead of "non-routine".

Meaning of specific quality standards

GMP for ATMPs is required, although there is some degree of flexibility how the inspectors will apply GMP.

The rules regarding the authorisation of the establishments (non-profit organisations and public establishments (hospitals) which are able to prepare these types of medicinal products and the

authorisation of the products) are defined by the 2012-1236 decree published on the 6th of November 2012.

The French regulations provide for a strict separation of drug production and their use (i.e. the delivery and administration). As such, it is not possible for a hospital infrastructure to claim the status of a pharmaceutical establishment, a notable exception being the Assistance Publique des Hôpitaux de Paris (AP-HP).

Therefore, even as the MTI-PP framework generally applies to all establishments, only hospitals, which cannot be pharmaceutical establishments in France, use it.

Documentation required

The submission of an application file (initial authorisation, modification of authorisation, renewal of authorisation) by the applicant establishment or organisation is made to the Director General of the ANSM.

The content of the dossier is set out in the Order of 4 February 2013. It defines a CTD-like document but with certain adaptions and other numbering changes. Annexes I to IV provide detailed information (in French):

- Annex I: Administrative information on applicant and procurement/manufacturing sites.
- Annex II: Description of the dossier for Application and/or renewal

Application form
Information about personnel and site(s)
List of critical materials (as per the table in the annex)
Third party activities
Information about transport
Documentation: Provision of a list of procedures for activities carried out within the establishment or organisation and, if applicable, the site, including a list of procedures in place where activities for scientific purposes are carried out on the same premises.

- Annex III: Application file for prior authorisation relating to substantial modifications to the authorised activities of an establishment like preparation, storage, distribution or transfer of ATMP prepared on ad hoc basis

e.g. Description of substantial modification of activity

- Annex IV: Application file for initial authorisation, renewal or modification for authorisation of an ATMP prepared on ad hoc basis ("product authorisation", CTD like but with adapted structure and numbering). The modules below refer to the requested dossier structure.

Module 1

  - SmPC, Labeling

Module 2: including Quality Information

  - Introduction, 2.S and 2.P,
  - P.9.1 to P.9.4: Specific sections for Medical devices, their essential requirements, compatibility with product,

- 2.X Specific information on certain product categories: 2.x.1 gene therapies and 2.x.2 Specific requirements for somatic cell therapy medicinal products and tissue engineered products

Module 3 : Information on non-clinical data

Module 4: Information on the clinical evidence for therapeutic use.

- Clinical study and other supportive data providing information on efficacy and safety
- Justification why the proposed therapy is a suitable to improve the patient's condition and that the treatment in question appears to be the only chance of avoiding a fatal outcome in the short term
- Justification of the fact that the medicinal product is likely to be of benefit to the patient and that the state of scientific knowledge suggests that it is effective and safe
- A RMP and PV-System

- Annex V: Virus safety information

Licenses required

An ANSM decision authorising the activity or rejecting the application for authorisation, renewal or modification of an MTI-PP, is drawn up following the conclusion of the assessment and the opinion issued by the ABM.

Two authorisations are needed:

- One authorisation (manufacturing license) for the establishment (MTI-PP establishment) and
- One authorisation for the product (either the MTI-PP clinical trial authorisation or the MTI-PP national authorisation, see explanation of categories below)

The authorisation, given for five years and renewable, consists of two parts:

- A decision describing the subject of the application, the opinion following the appraisal carried out and the opinion of the ABM,
- An annex describing the authorisation number, the name of the establishment or organisation, the address of its registered office, the address of the authorised establishment or organisation and the authorised activity(ies).

The ANSM publishes a regularly updated list of authorised MTI PP establishments or organisations (point III of article R. 4211-36 of the CSP). It includes the types of ATMPs applied to patients, but the list does not include specific product or indications.

In the list, two categories are provided: "MTI-PP á usage humain" which refers to establishments manufacturing a HE product based on a "national authorisation" and "MTI-PP à usage humain utilisé dans le cadre de recherche biomédicale" which refers to establishments manufacturing the same products within the scope of a clinical trial.

Tissue and blood establishments providing starting material are also required to have the usual licenses based on the respective EU Directives Directive 2004/23/EC for tissues and 2002/98/EC for blood.

5.2.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

Annual reporting is required and described in the Annex of the decision of 11/12/2019 (to be found on the MTI-PP site) on form and content of the annual activity reports of establishments or bodies authorised under Articles L 4211-9-1 (Manufacturing of MTI-PP through establishments or organisations, including health establishments) and 4211-9-2 (Manufacturing of ATMP through establishments or organisations, including health establishments) of the CSP (03/01/2020).

Information requested in this annex is summarised here:

A. Information about the Establishment:
   1) Administrative information of establishment or organisation
   2) Activities carried out within the establishment or organisation
   3) Description of relevant modifications during the year (in details see CSP 4211-45 and R4211-60)

B. Information about the Product
   1) Product-related information
      a) Such as the number of products which have been produced, details on differentiation steps and freeze-thaw cycles before administration, provision of products without final release data, use of non-dedicated equipment
   2) Manufacturing related information

C. Review of annual activities
   1) Raw/starting materials
   2) Final products
   3) Subcontracting activities

Pharmacovigilance

A PV-System and an RMP are to be provided as part of the application dossier in Annex 4 Module 4 for the MTI-PP. Reporting for Serious adverse reactions is required as for other medicinal products. SAEs are notified to the respective “centre régional de pharmacovigilance”.

Starting materials need to comply with Biovigilance (the vigilance process connected to the tissue and cells framework). This is expected to be the case for all EU countries (for comparison with Germany see chapter 5.1.2).

Traceability

As part of Annex 4 Module 2 of the application dossier, a description should be provided of the system that the holder of the authorisation referred to in Article L. 5121-1 (17°) of the Public Health Code intends to establish and maintain in order to ensure the traceability of each product, from its starting materials and raw materials, including all substances in contact with the tissues or cells that it may contain, to the patient.

5.2.3 PRODUCTS APPROVED UNDER A HOSPITAL EXEMPTION SCHEME

Overview

The ANSM publishes a list of Establishments or Organisations authorised by ANSM to carry out activities relating to MTI-PP (last dated 30/07/2020). This list currently includes eight Establishments (essentially hospitals). More details can be found on a poster analysing different aspects of public establishments that are manufacturing MTI-PP (dated 02/2019, on MTI-PP webpage) but also for so-called MTI expérimentaux (which "usually" are Advanced therapy investigational medicinal products (ATIMPs)) . The analysis is based on results of seven establishments (12 have been requested) and 11 products. The results apply to both groups (MTI-PP and MTI expérimentaux) but are still worth presenting here. At the time of publication of these data:

- 82% of theses product were autologous, the other 18% were of allogeneic origin.
- Similar distribution of systemic (54,2%) and local action (45,5%).
- 82% were SCTMPs, 9% TEPs and 9% GTMPs.
- More than half of them were in Phase I or II development phase (55%), 9% in Phase III and 9% already commercialised; 27% were not further identified.
- 91% of the MITI-PPs were administered to patients before final release.
- Five establishments produced more than three batches per year, with a maximum of 162 units.

According to a publication from 2015 (Bonnaud-Vrignaud et al. 2015), at that time 14 establishments had been authorised. That would be six more than provided in the list (30/07/2020, as above); however, the scheme is obviously still used in mostly early development.

Examples

The ATMP classes are mentioned in this list but no specific products, product types or indications.

As mentioned above the ANSM provides MTI-PP authorisations and MTI-PP authorisations in the scope of a clinical trial. According to the establishment list within such MTI-PP clinical trials, gene therapies are also tested.

Specific Indications or products excluded?

France seems to be one of the very few countries including Gene Therapies in the hospital exemption scheme; however, that seems to be the case only in the MTI-PP clinical trial setting. A CAR-T case is provided in the next chapter.

5.2.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

A complete legal framework has been established for Hospital exemption (MTI-PP), which partly extends beyond the EC requirement. As such, Applicants may apply for a clinical trial under the Hospital exemption regulation in France, which is unique

The ANSM states that clinical data justifying the therapeutic interest of the product may be fragmentary or even non-existent. In such cases, the absence of clinical data must be justified and the expected benefit for the patient must still be documented.

Where appropriate, clinical data may be based on results obtained in clinical trials using similar products for the same or similar indications.

In all cases, a safety and efficacy monitoring plan should be included in a risk management plan.

According to Chabannon and Larghero (2018, in French), this regulatory framework allows for the small-scale production of CAR-T cells in development, which have no licensed or marketed counterpart:

- because they are developmental CAR-T cells, which have no licensed or marketed equivalent,
- because they target tumour antigens other than those targeted by licensed and marketed CAR-T cells, or
- because the genetic modification of the T cells confers enhanced properties such as the integration of a suicide gene conferring increased safety in the event of a serious adverse event, or
- the simultaneous targeting of two tumour antigens to prevent certain resistance mechanisms, to name but a few opportunities.

5.2.5 SUMMARY

- The authorisation is issued by the ANSM. The ABM provides its scientific opinion.
- The ANSM has a comprehensive application procedure and documentation (similar to CTD but with a slightly different structure) for MTI-PP, this includes the initial approval, renewal and modification.
- HE are defined as ATMPs “prepared on an ad hoc basis” (“Médicament de thérapie innovante préparé ponctuellement”; MTI-PP).
- There are two MTI-PP categories: “MTI-PP á usage humain” based on a “national authorisation” and “MTI-PP à usage humain utilisé dans le cadre de recherche biomédicale" which refers to establishments manufacturing the same HE products within the scope of a clinical trial. The latter is unique in the EU.
- HE Authorisation is provided for 5 years; renewal is possible.
- Annual reporting is required.
- Establishments are published in a list (2020) which is publicly assessable. Both types of MTI-PP categories are included. The list does not include the specific product or indications.
- Specific details regarding the applications for both MTI-PP categories and investigational ATMPs (MTI expérimentaux) have been analysed and summarised in a poster (2019) on the ANSM’s website.
- France seems to be one of the very few countries including Gene Therapies in the hospital exemption scheme, but only in a clinical trial setting.
- Only public establishment and non–profit organisations apply, one reason being that they cannot be “pharmaceutical entrepreneurs” by law.

- The authorisation for MTI-PP seems to be regularly applied.
- MTI-PP can theoretically by law be imported and exported, however that has not occurred to date.

5.3 The Netherlands

The Ministry responsible for Hospital exemption approvals is the Healthcare and Youth Inspectorate (Inspectie Gezondheidszorg en Jeugd, IGJ).

5.3.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

The HE is implemented in the Netherlands law "Geneesmiddelenwet", article 40.3.d.

Definition of non-routine

As a guideline, applicants may consider the following to be non-routine and check with the NEB the number of possible products that can be applied to patients per year:

- ATMP prepared from autologous cells;
- ATMP prepared from non-autologous cells but specific to one patient;
- ATMP prepared on a small scale.

Meaning of specific quality standards

Volume 4, Part IV "GMP requirements for Advanced Therapy Medicinal Products", is applied.

Documentation required

An application for permission to prepare an ATMP based on a hospital exemption can only be submitted by, and granted to, a legal entity that is responsible for the production of the ATMP concerned. This may be 1) the manufacturer or 2) the hospital.

An (QP) Officer for Quality and release is required. The QP verifies that the ATMP is supplied on the basis of a medical prescription.

A specific application form (only available in Dutch), the "ATMP zonder handelsvergunning" (ATMP Hospital Exemption: request for pre-consultation) is provided on the IGJ website as basis for approval, amended by available documentation where applicable.

Consultation with the IGJ is recommended. During preliminary consultations the applicability of a hospital exemption for the product will be discussed as well as which documentation must be submitted.

During the preliminary consultation a general assessment will be made as to whether an application for a Hospital Exemption is likely to succeed. Subsequently, a formal application via the application form has to be submitted.

For a preliminary consultation some important topics are:

- A brief description of the ATMP and of the ATMP production/preparation.
- The circumstances in which the ATMP will be applied.
- Contact details, such as name, organisation, department, address, telephone and e-mail address.

The formal application includes (for details please check application form "aanfraagformulier", only in Dutch):

- Title and reason for application
- Information on patient group (detailed information required), medical need and existing alternative treatments,
- For an initial application: physicians' statement (extra annex), Quality documentation (such as an IMPD), Safety documentation, RMP
- For a renewal report (or if treatment was stopped prematurely):

Number of patients, results that were achieved with regards to safety and efficacy and if expectations were met,
PV: unexpected serious adverse effects and serious adverse events observed and frequency. The evaluation of safety should provide insight into which (serious) adverse events are (possibly) related to the ATMP and which complications are related to (progression of) the underlying disease.
Justification for follow-up application: same medical need or are there meanwhile better alternatives available.

- Details such as:

Intended starting date for manufacturing and treatment, location of preparation and treatment
Any scientific advice or MAA submissions
ATMP certification and/or ATMP classification at the CAT
Mode of action
Production on prescription for use in an individual patient

- Clinical trial information if existing: IB, IMPD if existing, reference to EudraCT, Number of patients, results.
- In the case of GTMP: information on the vector
- In the case of SCTMP/TEP: Autologous, allogeneic or combined.
- Details as in the IMPD/M3 (if that is not provided) such as:

Name of active ingredient, product, route and strengths
Cell origin: state Tissue establishment (EU code), description of cell procurement
Processing details and aseptic process validation
Cell stability, passaging
Cell characteristics and specifications
Differentiation status and others
Compliance to Phr. Eur. Monographs
Absence of viral contamination
Contamination reducing steps, sterility testing concept
Starting materials: TSE risk mitigation, Viral safety, Donor testing
Risk assessment for DNA technology

Stability/Shelf-Life

- For Combined ATMPs (i.e., those where a medical device is an integral part of the ATMP), the opinion of a Notified Body (NB) is to be included.

Licenses required

- Manufacturing license (manufacturer, hospital pharmacy), GMP certificate
- Establishment license for cells, tissues, blood donations

5.3.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

Pharmacovigilance

A responsible person for reporting is required; this must be provided in the application form.

Reporting of

- Unexpected serious adverse reactions/events should be reported immediately (within 48 hours) to the IGJ.
- Side effects and adverse events need to be monitored.

The applicant shall provide a report on adverse reactions and events to the IGJ as part of the annual renewal report (see above) and after termination of the treatment.

Also, an RMP is required, providing a positive benefit/risk.

Traceability

Material of human origin as starting material must meet the requirements for obtaining, donating and testing as stated in the law and regulations: With regard to traceability of the human material, it must carry at least a donor identification sequence/code (DIS/DIC) (European Code (SEC) for tissues and cells and unique identification numbers for donors and donations for blood) and GMP for ATMPs section 6.37 (i)) and for registered ATMPs DIS/DIC must be present on the outer packaging (section 6.20 (x)).

Human material should originate from a tissue establishment with an accreditation for Procurement, Donation, Testing (see EU Compendium).

5.3.3 PRODUCTS APPROVED UNDER A HOSPITAL EXEMPTION SCHEME

Overview

There is no externally available database for products authorised under the hospital exemption and no specific examples can be provided. According to an early EC Update on HE (EC Pharmaceutical Committee 2012), already by 2012 the Inspectorate had approved around five hospital exemptions.

A report titled "Future expectations for ATMPs" ("Toekomstverwachtingen over ATMP's") issued by the IGJ stated in 2017 that 11 HE applications have been submitted to IGJ since 2010. Extension of the HE was requested for six ATMPs. Some were extended more than once. Among the ATMPs with an HE were the following categories:

- Autologous tumour cells,
- Lymphocytes,
- Mesenchymal stem cells, skin cells, mononuclear cells, specific cells, specific T cells and tumour-infiltrating lymphocytes.

According to a publication from Coppens et al. 2017, six products were approved in the period 2009 to 2017. When comparing this with the information from the IGJ report, this corresponds to the number of extended requests in 2017.

Examples See under "Overview".

Specific Indications or products excluded?

Not assessable.

5.3.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

Formally no clinical data are required, but when available these should be provided and are taken into account. Presence of clinical data is not mandatory but clinical data in the target population will facilitate HE approval.

Notification of an ATMP with Out Of Specification (OOS) results, which is administered by the treating physician, must be reported online to IGJ via the website. Details are given in the respective form (only in Dutch).

A specific Physician's statement for an ATMP hospital exemption is required (Appendix 1 to application form), meaning that the physician takes on the responsibility for any risk associated with the treatment.

5.3.5 SUMMARY

- The Ministry responsible for Hospital exemption approvals is the Healthcare and Youth Inspectorate (Inspectie Gezondheidszorg en Jeugd, IGJ).
- An application for permission to prepare an ATMP can only be submitted by, and granted to, a legal entity that is responsible for the production of the ATMP concerned. This may be 1) the manufacturer or 2) the hospital.
- Clinical data are not mandatory.
- Defined number of products per year.
- HEs are generally given for products intended for last-line treatment, which rather include orphan or oncological indications rather than, for example, chondrocyte products.
- Comprehensive and detailed application form, but CTD/IMPD not mandatory.

- Consultation with IGJ in advance to the application is highly recommended.
- No transparent database and access to SmPCs.
- Does not seem to be used lately.
- Currently six products are approved.

5.4 United Kingdom

While the UK is no longer part of the EU, it was before and for a significant duration of time in order to provide a national HE or HE-like route for ATMPs, and the Medicines and Healthcare Products Regulatory Agency (MHRA) has significant experience with ATMPs.

The MHRA acts on behalf of the UK Government and applies two distinct pathways for unlicensed medicines; HE and the "Manufacturers Specials" scheme. The latter is based on Article 5 (1) of Directive 2001/83/EC. The MHRA is responsible for approval of HE and "Manufacturers Specials" licenses.

UK is included in this report according to the BAG's request.

5.4.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

The UK's legislation for implementing the ATMP Regulation, including the requirements that apply under the Hospital exemption scheme, was laid out in the UK Parliament on 26 July 2010 and came into force on 19 August 2010. A link to the guidance summarising "UK's arrangements under the hospital exemption scheme" is provided.

The MHRA has two schemes for unlicensed medicines: the Hospital exemption and the UK "specials" scheme set up under the derogation permitted in Article 5 (1) of Directive 2001/83/EC.

Hospital exemption

The UK Hospital exemption applies for ATMPs that are prepared on a non-routine basis and are used in a hospital with a prescription for a specific patient.

The HE guidance refers to the ATMP Regulation (EC) No 1394/2007 and especially mentions that manufacture of ATMPs under the hospital exemption must be authorised by the Member State (the MHRA in the UK). In addition, traceability, quality and pharmacovigilance standards for ATMPs made under the exemption must be equivalent to ATMPs for which a centralised market authorisation would be granted by the EMA. Further §28 (2) of the regulation is referred to.

HE is also called "Manufacturers license exempt Advanced Therapy medicinal products (MeAT)" which is the more frequently used term.

A specific "Guidance on the UK's arrangements under the hospital exemption scheme" has been issued with detailed information on the process and documents.

Specials

"Specials" are products, not restricted to ATMPs, that have been specially manufactured or imported for the treatment of an individual patient after being ordered by a:

- doctor
- dentist
- nurse independent prescriber
- pharmacist independent prescriber
- supplementary prescriber

They can be supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised healthcare professional and for use by an individual patient under their direct personal responsibility.

An unlicensed medicinal product may only be supplied in order to meet the special needs of an individual patient. An unlicensed medicinal product should not be supplied where an equivalent licensed medicinal product can meet the special needs of that patient. Responsibility for deciding whether an individual patient has "special needs" which a licensed product cannot meet should be a matter for the doctor, dentist, nurse independent prescriber, pharmacist independent prescriber or supplementary prescriber responsible for the patient's care. Examples of "special needs" include an intolerance or allergy to a particular ingredient, or an inability to ingest solid oral dosage forms. Manufacturers (often hospitals but not necessarily) apply for a specials license from the MHRA, which must be satisfied as to the existence of a special need for the unlicensed medicinal product. MHRA expects that documentary evidence of this special need should be obtained by manufacturers, importers or distributors and that this evidence should be made available on request of the Licensing Authority.

The unlicensed status of the product needs to be declared on the product's packaging. Reimbursement needs to be checked with healthcare providers.

The manufacturer or assembler of "specials" must hold a Manufacturer's "Specials" License granted by the MHRA. A Qualified Person (QP) is not required to be named on a Manufacturer's "Specials" License for release of a finished unlicensed product. Release of "specials" should be by the Quality Controller or a nominated deputy.

For more details on "Specials" please refer to MHRA guidance.

Unlicensed products, whether under the "Manufacturers Specials" or a MeAT (Hospital Exemption, HE scheme) manufacturing authorisation do not require a product assessment as is the case in most other EU countries, as such assessment is not required under Human Medicines Regulations, HMRs (which are derived from 2001/83/EC Articles 5(1) and 3(7)).

The two schemes are compared in the following table (page 3 of the guidance):

Table 1: Summary of the main differences in scope between the HE and the "Specials" scheme

Hospital Exemption	**"Specials" Scheme**
Only applicable to ATMPs	In principle applicable to any product
The ATMP must be prepared and used in the same EU Member State	Products meeting the requirements of the scheme can be manufactured in the UK or imported to the UK
The ATMP must be commissioned by a medical practitioner	Products can be prescribed by doctors, dentists and supplementary prescribers
The ATMP must be custom made to meet an individual prescription and preparation must be on a "non-routine basis"	There is a special needs test (interpreted to mean the absence of a pharmaceutically equivalent and available licensed product).
The ATMP must be used in a hospital	There is no stipulation as to location

Definition of non-routine

The MHRA issued a specific "guidance on non-routine":

In the aforementioned guidance it is outlined that "…it is not feasible to provide a simple numerical formula that would delineate the boundary between routine and non-routine production". The MHRA will consider for their decision:

1. the product under consideration and
2. the scale and frequency of preparation of a specific product.

For example, with regards to the *product under consideration* the document outlines that if a specific operator is producing a specific product, any modification will probably be considered as another product.

The MHRA will further consider the product's mode of action and its intended use (indication, mode of administration, presentation i.e. liquid, powder, pre-filled syringe etc.), as well as the manufacturing processes used to generate the final product, any product intermediates or product specific starting materials (i.e. genetically modified retrovirus used to transduce patient specific stem cells), that are required.

With regards to *scale and frequency of the preparation* of a specific product, aspects to be considered may include: the overall numbers of the particular product prepared by the operator, the regularity and frequency of production, and the time period over which the preparation of that product has become established.

Accordingly, there could be a low scale/number of a specific product in the beginning which would increase over time. The MHRA would determine in a period of one to three years if it would be considered routine. If the same product is manufactured on a low scale and not regularly it might take longer before it could be regarded as routine. A large production scale on the other hand could be regarded as routine within one year.

The operators planning a HE application are encouraged to seek advice from MHRA to discuss applicability.

Meaning of specific quality standards

ATMPs made and used under the exemption must comply with the principles of GMP for ATMPs.

No QP is required (for neither HE authorisations nor Specials) but MHRA does require that the Quality Controller conduct the release activity to verify compliance with GMP, the Human medicines regulations, the prescription against which the product is manufactured and relevant pharmacopoeial monographs.

GMP is to be applied appropriately in line with the nature of the products involved.

The MHRA will list the particular category of ATMPs (gene therapy, somatic cell therapy or tissue engineered product) but not individual products in line with current manufacturer's licensing arrangements (see Nr 12 of Guidance).

Documentation required

For the HE essentially the manufacturing license is required. In addition to the manufacturing license itself, Labelling and a Package Leaflet (see No. 20 and 21 of guidance) are required.

Application is made via a form (for more details see next chapter on "licenses required").

Licenses required

For "MeAT" the following licenses are required:

- Manufacturer's license permitting manufacture of ATMPs under the hospital exemption; link for the form provided (under "manufacture of unlicensed ATMP"). Details on the ATMP manufacturer as well as contract laboratories, type of ATMP, name of quality controller, production manager and other administrative details are required.

The license includes GMP and sites will be inspected
However, no formal QP is required (neither for HE or for "Specials" license, [see Guidance Nr. 7])
Further labelling and package leaflet needs to be provided acc. to the guidance.

- In the case of ATMPs the Human Tissue Authority (HTA) regulates the donation (i.e. consent, donor selection and testing), procurement and testing of tissues and cells used in the manufacture of ATMPs. However, the manufacturing process following procurement and removal of tissues and cells from a tissue bank is regulated by the MHRA.
  Therefore, a license from the HTA is required for: consent, donor selection, donor testing, procurement (collection), processing, storage, distribution and import and export.
  The competent authority for blood as starting material is the MHRA.
- A wholesale dealer would need a wholesale dealer's license.

Sites that are authorised to manufacture unlicensed medicines are listed on the MHRA website.

5.4.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

The Applicant must provide a yearly update including:

- A description and number of batches and units manufactured in each of the three categories of ATMPs for which a manufacturer's license has been granted. The MeAT license can cover several products.
- An interim Compliance Report where there is significant change in the scale and/or scope of manufacture should be included.
- Inspection will take place based on associated risks (MHRA is referring to ICH Q9 principles).

No information on efficacy or safety in advance of approval is formally requested.

Pharmacovigilance

License holders (Manufacturers and Importers) need to record any adverse reactions to an ATMP and notify the MHRA of any suspected serious adverse reactions (2012 The Human Medicines Regulations). The MHRA might request a risk management plan from the manufacturer based on a case-by-case decision at the time of license application. The risk management plan should then provide details of the system in place to identify, characterise and minimise any risks related to the product. No reference to a specific RMP form is provided.

The clinician/medical practitioner using the ATMP will be required to record all adverse reactions and report serious adverse reactions to the MHRA.

Reports should be submitted electronically via ICSR Submissions (replacing the EudraVigilance website, EVWEB) or the MHRA Gateway. Prescribers and pharmacists supplying "specials" should report ADRs using a Yellow Card form or an electronic Yellow Card, stating the manufacturer and indicating that the product is unlicensed.

Traceability

The traceability provisions that will apply include compliance with the requirements laid down in Article 15 of the ATMP Regulation as well as the traceability requirements under the Tissues and Cells Directive (2004/23/EC) and the Blood Directive (2002/98/EC) (Guidance No. 14 and 15). That means that the hospital in which the ATMP is used will be required to establish and maintain a system for patient and product traceability containing sufficient detail to enable traceability between recipients of ATMPs and donors of the tissues and cells used in their manufacture.

5.4.3 PRODUCTS APPROVED UNDER THE HOSPITAL EXEMPTION SCHEME

Overview

Sites that are authorised to manufacture unlicensed medicines are listed on the MHRA website. Since the MS ("Manufacturers Specials") or a MeAT (Hospital Exemption, HE scheme) manufacturing authorisation do not have a product assessment there are no SmPCs available.

Up to 2012 there was no Hospital exemption approval but 18 authorisations to manufacture and supply unlicensed under ATMPs "Specials" terms (according to EC update 2012 (EC Pharmaceutical Committee 2012)). Three publications state that there were no HE authorisation at least up to 2018 (Goula et al. 2020; Ivaskiene, Mauricas, and Ivaska 2017; Coppens et al. 2020). Any MeAT authorisation would be listed in the aforementioned document.

Examples

According to several publications there are no HE approvals at least up to 2018 (Goula et al. 2020; Ivaskiene, Mauricas, and Ivaska 2017; Coppens et al. 2020).

Specific Indications or products excluded?

This is not assessable since no licenses are currently issued. No exclusions based on ATMP type or indication are expected, especially as products are not assessed.

5.4.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

According to the regulation, the HE products are prepared and used within the same member state; i.e., the HE is intended as a purely national solution, and import and export is not foreseen. Accordingly, if a manufacturer or prescriber wants to provide patients outside of UK with a product, it cannot be manufactured under the HE, but products under the specials license can be imported and exported to EU/EEA countries.

Practically, prospective applicants/manufacturers will approach the MHRA, for example through the Innovation Office, to discuss their plans for a new manufacturing authorisation or to amend an existing authorisation.

Apart from the Specials scheme, the UK also introduced the early access medicine scheme (EAMS) in 2014, which is a true approval pathway to provide specific innovative medicines for patients in the UK.

EAMS aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. This pathway is more interesting to commercial applicants and not restricted with respect to manufacturing number. It is more likely to be a step towards a later MAA.

Under this scheme, the MHRA will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available when the EAMS submission was made. The opinion lasts for a year and can be renewed.

The scheme is voluntary and the opinion from MHRA does not replace the normal licensing procedures for medicines.

The scientific opinion will be provided after a 2-step evaluation process:

- The promising innovative medicine (PIM) designation.
- The early access to medicines scientific opinion.

A CTD dossier corresponding to an MA dossier needs to be provided, including labelling, PV-System, RMP as well as a protocol to accompany the treatment according to the authorised SmPC.

There should be early clinical data available for PIM designation. For more details please see the MHRA website.

5.4.5 SUMMARY

- The UK has two specific processes in place, both based on relevant EU legislation: A HE provision (MeAT) for ATMPs, and a Manufacturer's Specials provision not restricted to any product type.
- No product-specific licenses are issued.
- The HE approach is based on a manufacturing license per ATMP group plus labelling and PIL.
- No additional extensive documentation is required, which makes the scheme fast and easily accessible.
- Applicants (doctors) appear not to favour HE use. They rather use the "Specials" scheme which includes an import/export option.
- Currently there appear to be very few products licensed under MeAT.
- MeAT licenses would be included in the existing database, "register of licensed manufacturing sites".
- GMP and QC is required but no formal QP.
- Quality (GMP) is inspected and risk is assessed on a case-by-case decision.
- Control of risk is via usual safety reporting and annual reporting measures.
- Another early access option for patients with life threatening or seriously debilitating conditions is authorisation according to Early Access to Medicines Scheme (EAMS).

5.5 Sweden

5.5.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

The National Competent Authority responsible for granting hospital exemptions and manufacturing licenses is The Medical Products Agency (Läkemedelsverket).

The Hospital exemption is regulated in "The Medical Products Agency Regulation ("Läkemedelsverkets föreskrifter" LVFS 2011:3) on medical products for which hospital exemptions apply".

The following definition is provided in the Swedish Medical Law (läkemedelslagen) 1992:859.

- Prepared in Sweden according to a non-routine procedure,
- Specially adapted for one individual patient,
- According to one doctor's orders/prescription,
- Used in Swedish hospital(s).

A decision tree (Appendix 1 of the guidance) similar to the PEI's (see Germany) provides guidance for applicability of the HE Framework.

The HE manufacturer can be either a company or a hospital where the patient is treated, both in Sweden.

Definition of non-routine

There is no official definition available. The assumed number of patients needs to be provided in the application.

Meaning of specific quality standards

GMP for ATMPs according to Eudralex Volume 4. A QP for release is required.

Documentation required

The required documentation is listed in the respective document ("Ansökan om tillstånd för tillverkning av läkemedel som omfattas av sjukhusundantaget enligt 8 kap. 2 § Läkemedelslagen (2015:315)"). A specific application form needs to be filled out (only Swedish) to apply for the manufacturing of an ATMP. It is based on the MPA's regulations (LVFS 2011:3).

It must include:

- Contact details (name, organisation, address) of applicant,
- Proof of registration if applying from a business,
- Information on the pharmaceutical formulation of the medicinal product,
- Address for the site of manufacture/quality control,
- Description of site and equipment, and activities
- Description of any contract work that will be done and copy of contract(s) and manufacturing permission, including imports and exports,
- The applicant is expected to provide a description of the manufacturing process which is used for all batches included in the HE application. This shall also include a description of properties and biological activity. Process controls and predefined specification need to be provided. The documentation shall contain a risk assessment of known risk factors, such as potential infectious agents, immunogenicity, tumorigenicity, altered cell function, cell and non-cell related contaminants. For gene therapy products additional information is requested such as content of replicable viruses and integration of retro/lentiviral genome (see also Chapter 2 of the EU GMP for ATMP).
- Information on hospital(s) where the product will be used,
- Information on how many patients will receive the product,
- Summary of product characteristics (Appendix 1 of LVFS 2011:3),
- Information if the ATMP contains a medical device, (the medical device must meet the essential requirements according to the medical device requirements LVFS 2003:11, English form),
- Information on supplier of tissue and cells and information regarding use of tissues/cells for manufacturing & copy of permission for use,
- A description of the measures that are planned to ensure follow-up of the (side) effects of the product, including risk management system that will identify, characterise, prevent and minimise the risks associated with the product
- An organisational plan that shows responsibilities, authorities & reporting obligations,
- Nomination of Qualified Person and qualification/experience.

The information on manufacturing control should ideally be provided in an IMPD-like format. A detailed guideline (only Swedish) outlining the desired quality information has been published. Regarding the format, it includes references to Ph.Eur. Monographs.

The application form must further include the SmPC, which includes details on safety, clinical details and pharmacological characteristics.

A clinical proof of efficacy is not specifically requested. It is assumed that the decision for an authorisation will be made based on the available information such as the SmPC, RMP and supportive nonclinical and clinical data if available.

The decision on authorisation to manufacture medicinal products covered by the hospital exemption must be taken by the competent authority within 120 days. The authorisation is usually valid for a maximum of five years and only valid for the specific product. A written approval is required in case of substantial changes to the original application.

Licenses required

All manufacturers of medicinal products in Sweden must have an authorisation for Manufacturing (and Import) from Läkemedelsverket. Manufacturing must comply with GMP and the manufacturer must have at least one Qualified Person who is responsible for the medicinal product being manufactured. Prior to issuing a manufacturing authorisation for a new operation, Läkemedelsverket will carry out an inspection of the company site, covering for instance, equipment, premises and quality systems. The manufacturer is inspected by GMP inspectors to assure the compliance with the EU GMP Part IV regulations. The manufacturing process including the QC activities as well as the release procedures are handled in the same way as for other products. Inspections will subsequently be conducted on a regular basis.

The Medicinal Products Ordinance (2015:458) states that a manufacturing authorisation is limited in time and may be subject to conditions. (HSLF-FS 2016:32). Changes need to be reported and approved by the Agency. The original HE Manufacturing license costs SEK 100.000 (about 10.155 CHF, Chapter 2 Application fees §9a). The annual fee is SEK 30.000 per manufacturing authorisation (3.046 CHF, Chapter 4 Annual fees §3).

If a company is applying for hospital exemption, they must send proof of registration ("registreringsbevis") that they are an authorised Representative/Manufacturer with the application form.

If tissues/cells are procured to be used as starting material in manufacturing of medicinal products, an authorisation to operate as a tissue establishment must be applied for (sent to Läkemedelsverket). If the tissue establishment is to export or import tissues and/or cells to/from a country outside the EEA, an export/import permit is also required.

All necessary licences are summarised in Chapter two of the HE guidance.

5.5.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

In the specific HE guideline (only Swedish) several flow-charts are included that explain in detail legislations, involved agencies and flow of activities for Traceability (Appendix 2) and PV reporting (Graph 3).

Pharmacovigilance

The holder of a marketing authorisation for a medicinal product must have a PV system described in a PV system master file (PSMF). PV systems are inspected by Läkemedelsverket.

The holder of the manufacturing authorisation for medicinal products with hospital exemption should have a qualified person who is responsible for safety monitoring of the medicinal product (LVFS 2012:14). The responsibilities of this expert are set out in the Medical Products Agency's regulations (LVFS 2012:14) on pharmacovigilance of medicinal products for human use. (HSLF-FS 2016:32).

(HSLF-FS 2016:32) Chapter 5 2 § requires that the manufacture of the medicinal products covered by the hospital exemption shall comply with the requirements imposed on the holder of a marketing authorisation pursuant to the Medical Products Agency's regulations (LVFS 2012:14) on pharmacovigilance of medicinal products for human use. Suspected serious and non-serious side effects must be reported to the Eudravigilance database with the exception of the reporting requirement under § 9(1) concerning reporting of adverse reactions occurring in third countries.

A reporting scheme is provided in Appendix 3 and the reporting template in Appendix 4 of the HE guideline (only Swedish).

The periodic safety update reports shall contain an evaluation of the effectiveness of the risk management system established for the medicinal product. (HSLF-FS 2016:32).

Traceability

According to LVFS 2004:6 on GMP, all stages in the manufacturing process for medicinal products must be documented and full traceability needs to be ensured. The manufacturer must have, and maintain, a traceability system and ensure that the medicinal product and its starting materials – including everything that comes into contact with the tissues/cells they may contain – can be traced in terms of origin, manufacturing, packaging, storage, transport and delivery to the hospital where the product will be used.

If the medicinal product contains human tissues or cells (other than blood cells), the traceability system must also meet the requirement of LVFS 2008:12 on handling of human tissues and cells in medicinal manufacturing. If the product contains human blood cells, the system must meet the requirement of LVFS 2006:16.

The manufacturer of the medicinal product should retain the details that are needed for full traceability for at least 30 years from the use of the product. In the event of bankruptcy or liquidation of the manufacturer, the necessary data for full traceability is transferred to the hospitals that used

the medicinal products. This is required even if the authorisation to manufacture the product is removed. The requirements are based on the GMP for ATMPs chapter 6.6.

5.5.3 PRODUCTS APPROVED UNDER A HOSPITAL EXEMPTION SCHEME

Overview

No statistics or information is available on the Agency's site.

Based on the EC Report from 2012, in Sweden two types of products (mesenchymal stem cells for Graft versus Host disease and a chondrocyte implantation product) were identified that can be considered legally on the market although no formal decision was made.

According to Eder and Wild (2019), chondrocytes, mesenchymal stem and stromal cells, foetal stem cells and keratinocytes are approved.

No GTMPs are approved under HE.

Examples

See under "Overview".

Specific Indications or products excluded?

Not assessable.

5.5.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

N/A

5.5.5 SUMMARY

- The national authority responsible for granting hospital exemptions and manufacturing licenses is Läkemedelsverket (The Medical Products Agency).
- A Hospital exemption is based on a product-specific manufacturing license, which is valid for five years.
- A comprehensive application form needs to be filled out for HE approval. The application form focuses on manufacturing information.
- No specific proof for efficacy is requested (case-by-case decision).
- GMP including a QP is required.
- Importation of starting materials is allowed.

5.6 Spain

The Spanish Agency for Medicines and Health Products (AEMPS) is responsible for granting Hospital exemptions for ATMPs.

The AEMPS also established a Spanish Committee for Advanced Therapies. This is a multidisciplinary team, made up of experts from different specialties. The aim of this group is to discuss and raise awareness of the regulatory situation of the various ATMPs, in order to contribute to the procedures affecting this type of medicinal product.

Spain has been chosen for inclusion in this report for two reasons: the country has a very detailed and transparent process for hospital exemption, and there was also an approval of a CAR-T via HE. This seems to be the only approval for a CAR-T granted under HE (Juan et al. 2021).

The documents are provided only in Spanish.

5.6.1 SUMMARY OF LEGAL AND REGULATORY FRAMEWORK

Hospital exemptions for ATMPs are granted by the Spanish Agency for Medicines and Health Products under Royal Decree 477/2014, of 13 June which regulates the authorisation of non-industrially manufactured ATMPs.

The hospital exemption (HE) allows for the use of ATMPs under special conditions. The HE is only applicable to individual patients treated in the hospital setting; HE is mainly conceded to the academic centers that developed the ATMP.

It shall be mentioned that the AEMPS distinguished two HE cases:

- Those that can be applied for after completion of first clinical trials and accumulation of sufficient evidence of quality, safety and efficacy to apply for a use authorisation when this evidence becomes available.
- Those called “uso consolidado” (”well-established use”). As defined in article 2.2 of the royal decree: "Advanced therapy medicinal products for established use: those advanced therapy medicinal products for which it has been demonstrated that they have been in regular use in a specific hospital institution before the entry into force of this royal decree.” Those hospitals have been able to send an intent to submit before 15 October 2014 and the application during the following 6 months. This possibility does not exist any longer.

All details for advanced therapies and specifically for HE are provided on the AEMPS’ website (only HE topics mentioned):

- ROYAL DECREE 477/2014, of 13 June, regulating the authorisation of advanced therapy medicinal products of non-industrial manufacture. (BOE no. 144, of 14 June)
- Document of questions and answers on the Royal Decree 477/2014, of 13 June which regulates the authorisation of medicines of advanced therapy of non-industrial manufacture.

- Procedure for the application for authorisation of use of advanced therapy drugs, as established in Royal Decree 477/2014, of June 13, 2014 regulating the authorisation of advanced therapy medicinal products of non-industrial manufacture (published on 9 June 2015).
- Communication from the Pharmacovigilance Contact Person (for ATMPs in general and for HE, see for further information on PV in section 5.6.2).
- Independent Clinical Research Support Office: Here researchers and promoters can generally receive advice on technical and scientific aspects of a regulatory nature or on administrative and practical aspects.

Definition of non-routine

No specific definition or number of batches per year is provided.

Meaning of specific quality standards

Entities that manufacture medicinal products that have authorisation for use must be certified in GMP and their scope of certification must include the production process of the authorised medicinal product.

The use restricted to one institution or hospital

Use is restricted to an institution or hospital (Art 3, Royal Decree 477/2014). This institution or hospital receives the HE approval. However, manufacturing can be done by any other authorised manufacturer as provided in the dossier. Changes to the manufacturing site need to be evaluated through submitting a variation to the AEMPS.

Several institutions can apply for separate use authorisations with ATMPs produced by the same manufacturer.

A manufacturer that is not a hospital and wishes to develop its own ATMP is not eligible for this use authorisation procedure and will have to apply for an authorisation procedure through the EMA centralised procedure.

Documentation required

A summary of the guideline for documentation is provided below.

The application for authorisation of use shall be submitted to AEMPS and must contain all the information specified in Chapter II, Authorisation of Use of advanced therapy medicinal products, of the Royal Decree, as summarised below.

The content of the request for authorisation is described in Art. 5 of Royal Decree 477/2014. The application for authorisation of use shall be submitted electronically to the AEMPS and shall include the following information:

- Application letter.
- Application form: Needs to be submitted through the RAEFAR (= AEMPS Registry database, for which it is necessary to have a Digital Certificate, user and password authorised by the AEMPS). The eAF form is accessible under: Sede Electrónica de la Agencia Española de Medicamentos y Productos Sanitarios - Sede Electrónica de la AEMPS ("Autorización de comercialización de medicamentos de uso humano, de fabricación no industrial, para Uso Terapeutico (Terapia Avanzada) (eAF)").
- Technical dossier: NEES (Non-eCTD electronic Submission) format dossier that will include the technical documentation supporting the application. This includes:

CTD dossier (acc. to Volume 2B: "Notice to Applicants. Medicinal products for human use. Presentation and format of the dossier Common Technical Document (CTD)"). The content should follow the Guideline on human cell-based medicinal products (EMEA/CHMP/43) and the general guidance documents provided on the AEMPS ATMP site should be considered.
Qualified person responsible for pharmacovigilance, as well as the necessary infrastructure in Spain for reporting any adverse reactions which are suspected or occurring in Spain, or in a third country (point ñ) of Article 5(1) of RD 477/2014.

The application must further include an SmPC, Labelling, and Patient Information.

The application shall be submitted in Spanish but parts of the scientific-technical documentation may be submitted in another language.

The maximum period for assessment of the authorisation for HE shall be 210 calendar days, which shall begin to run from the day following the date of submission of a valid application.

The authorisation has an initial validity of three years and may be renewed periodically. This process is described in Art. 10 RD 477/2014. Renewals of the authorisation shall be valid for five years.

A very helpful Q&A Document is provided on the AEMPS site (Spanish).

Further, for information, there is also a Naming convention for ATIMPS (EN) established. However, the relevance for HE is not clear.

Licenses required

A GMP Manufacturing license (article 8 of RD 477/2014) is required for the manufacturing facility.

Additional to the manufacturing licenses, the patient information document intended for the patient must be part of the informed consent sheets that each hospital institution has approved by their respective Care Ethics Committees for each of the procedures in which an ATMP is administered.

5.6.2 MONITORING FOR PHARMACOVIGILANCE AND PROOF OF EFFICACY

The HE follows strict standards of traceability, pharmacovigilance, and quality. Based on the Spanish legislation on ATMPs (RD477/2014), February 2021, there is a clear requirement for clinical data on efficacy and safety before any HE authorisation.

Annual report

The annual report (Royal Decree 477/2014, article 13) shall include the number of batches of each of the ATMPs of which they are holders. The annual report shall be submitted one year after the date corresponding to the decision on authorisation for use. Holders must also report production incidents that may have occurred during that period.

Pharmacovigilance

Royal Decree 477/2014, article 12, states that "The responsibility for pharmacovigilance will be of the hospital institution holder of the authorisation of use, which must be communicated to the Spanish Agency for Medicines and Health Products, as well as to the competent bodies in the field of pharmacovigilance of the autonomous community where it has its headquarters, the name of the person responsible for this activity." A PV System is required.

Further, "The holder of the marketing authorisation must have in Spain, permanently and continuously, a contact person in the field of pharmacovigilance, and will communicate to the Spanish Agency for Medicines and Health Products the contact details of the same through an electronic system that will be provided for this purpose. The designated person shall possess the appropriate experience and training for the performance of his or her duties. The Spanish Agency for Medicines and Health Products will maintain a database of these people, which will be available to the competent bodies of the autonomous communities." (Article 14, RD 477/2014).

A manual for that process can be accessed via webpage.

The AEMPS may request a risk management plan at any time.

The AEMPS has also developed a computer application that allows marketing authorisation holders of any medicinal product and hospital institutions holding authorisation for ATMPs of non-industrial manufacture to register and update the pharmacovigilance contact person's data. A manual can be accessed on the webpage.

More detailed information and examples can be found in the Q&A document relating to Article 12.

Traceability

Details of Traceability are provided in Article 11 RD 477/2014. The general rules in accordance with Article 15 of Regulation (EC) No 1394/2007 apply.

Further requirements for traceability for cell and tissues as well as blood are provided in Royal Decree 1301/2006, of November 10, which establishes the quality and safety standards for donation, obtaining, evaluation, processing, preservation, the storage and distribution of human cells and tissues. The rules of coordination and operation for their approved use in humans, where appropriate, are based in Royal Decree 1088/2005, of September 16, which establishes the technical requirements and minimum conditions of blood donation and transfusion centres and services. Generally, these regulations reflect EU Directives 2004/23/EC and 2002/89/EC.

More detailed information and examples can be found in the Q&A Document relating to Article 11.

5.6.3 PRODUCTS APPROVED UNDER A HOSPITAL EXEMPTION SCHEME

Overview

The list of authorised HE in Spain is published on the AEMPS website and includes a reference to the respective SmPC (see Figure 3):

NOMBRE	TITULAR DE LA AUTORIZACIÓN DE USO	FECHA AUTORIZACIÓN DE USO	FICHA TÉCNICA
NC1- SUSPENSIÓN CELULAR EN PLASMA AUTÓLOGO 100-300×106 CELULAS- HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA, 1 jeringa precargada	HOSPITAL UNIVERSITARIO PUERTA DE HIERRO MAJADAHONDA	29-01-2019	FT Ficha técnica pdf
ARI-0001 DISPERSION PARA PERFUSION QUE CONTIENE 0,1-1×10^{8} CELULAS/KG – HOSPITAL CLINIC DE BARCELONA	HOSPITAL CLINIC BARCELONA C/Villaroel, 170 Barcelona	01-02-2021	FT Ficha técnica pdf

Figure 3: List of authorised HE in Spain as published on the AEMPS website

Examples

These two products were authorised quite recently:

1. NC1: Autologous mesenchymal stem cells from bone marrow, (SCTMP, link to SmPC)

Description: Autologous bone marrow-derived mesenchymal stem cells.

The active substance of this medicinal product are the autologous adult mesenchymal stem cells from expanded bone marrow at a concentration of 100,000 cells/µl.

It is administered intrathecal via a microinjection system as a suspension for injection.

Indication: NC1 is indicated for the treatment of adult patients (≤65 years) with sequelae of chronic traumatic spinal cord injury with incomplete traumatic spinal cord injury, with incomplete dorsal or lumbar spinal cord injuries.

Complete dorsal or lumbar spinal cord injuries are excluded, with the exception of cystic localised complete lesions, with a medullary cavity extending no more than 1-3 spinal segments.

Challenges: The mechanism of action has not been fully understood. One possible mechanism of action, based on results of in vitro experiments, would be neural differentiation of the cells contained in the NC1 drug upon contact with soluble factors provided by glial cells, a phenomenon called biological transdifferentiation.

These in vitro findings are confirmed by preclinical in vivo studies of transdifferentiation of allogeneic MSCs from male donors into traumatised nerve tissue of female recipients. It is concluded that after transplantation of ESCs into traumatic Nervous System lesions, they can be identified in the long term (at least over the course of 4 months) and show signs of phenotypic differentiation to nerve cells, mainly neurons and astrocytes.

Data from human studies have been provided: One trial with 12 patients with complete spinal cord injury and another 10 patients with incomplete spinal cord injury have been studied.

2. CAR-T

The product ARI-0001, a new autologous chimeric antigen receptor (CAR) targeting CD19, was approved in 2021 by AEMPS under HE for adult patients over 25 years of age with relapsed or refractory CD19+ acute lymphoblastic leukaemia (SmPC).

Description: ARI-0001 is a dispersion for infusion, containing 0.1 – 1 x 10^6 cells/kg.

ARI-0001 (also called CAR-transduced T-lymphocytes with CAR ANTI-CD19 (A3B1)4-1BB/CD3ζ)) is a product classified as an advanced therapy - gene therapy due to the fact that the active substance is autologous differentiated T-lymphocytes from peripheral blood, expanded and transduced with a lentivirus to express a chimeric

antigenic receptor with anti-CD19 specificity (A3B1) conjugated to the 4-1BB and CD3ζ co-stimulatory regions.

Indication: ARI-0001 is indicated for the treatment of relapsed or refractory CD19+ B-cell acute lymphoblastic leukaemia (ALL) after at least two lines of treatment or CD19+ B-cell ALL in relapsed or refractory after a minimum of two lines of treatment or in post-transplant relapse in adult patients over 25 years of age.

Challenges: The decision of the AEMPS was based on the documentation of the efficacy and safety of ARI-0001 from the CART19-BE-01 clinical trial, designed to evaluate ARI-0001 in the most common CD19+ B cell malignancies (acute lymphoblastic leukaemia [ALL], chronic lymphocytic leukaemia, and non-Hodgkin's lymphoma [NHL]). The trial was approved by Hospital Clinic's Review Board in February 2017, and by the AEMPS in May 2017. The AEMPS considered that the results were most convincing in patients over 25 years of age with relapsed or refractory (R/R) ALL, thus becoming the indication approved as HE.

Specific Indications or products excluded?

The above examples show a somatic cell therapy and a gene therapy medicinal product have been approved via HE. There is no reason to expect that TEPs could not be approved as well.

From the two authorised products it may be deduced that only products for high medical need without therapy option will be considered under HE.

5.6.4 CHALLENGES AND SOLUTIONS FOR PRODUCTS

Before the ATMP Regulation and the respective Spanish Regulation came into effect, there have been products which have been used in some hospital institutions, which were not considered medicines at the time. These hospital institutions must obtain an authorisation from the Spanish Agency for Medicines and Health Products (refer to section 5.6.1). A transition period for such products was defined. Among these products were autologous transplantation of chondrocytes, the implantation of keratinocytes for the treatment of burns or the treatment of corneal lesions with limbocorneal stem cells. These products are no longer listed under the HE approvals.

It is worth noting that the authorisation of the products are exempted from the payment of fees.

Developed as a non-industrially manufactured product with the same quality and safety standards as the European ATMP regulation, ARI-0001 was conditionally authorised because it addressed an unmet medical need, i.e., treatment of ''adults'' (over 25 years old) with R/R ALL. Although Kymriah (tisagenlecleucel, developed by Novartis) was authorised by the FDA and EMA for R/R ALL patients under 25 years of age, adults with R/R ALL also have a dismal prognosis, and ARI-0001 therefore offers a therapeutic option them.

This approval allows for the use of ARI-0001 (outside of clinical trials or compassionate use programs).

5.6.5 SUMMARY

- The Spanish process and description of documentation for a hospital exemption is very detailed and transparent; electronic submission is required.
- The AEMPS also established a Spanish Committee for Advanced Therapies.
- Hospitals can apply for an HE for their product after completion of first clinical trials and accumulation of sufficient evidence of quality, safety and efficacy to apply for a use authorisation.
- The regulation defines an “uso consolidado” (”well-established use”) which was valid for products falling under the definition of an ATMP which have been in use before the regulations came in place. Among these products have been autologous transplantation of chondrocytes, the implantation of keratinocytes for the treatment of burns or the treatment of corneal lesions with limbocorneal stem cells. This possibility has now ceased.
- The use is restricted to an institution or hospital.
- Manufacturing can be done by any authorised manufacturer as provided in the dossier.
- Authorisations for HE products are exempted from the payment of fees.
- An annual report is required.
- Patient informed consent sheets need to be approved by the hospital institutions’ Ethics Committees.
- The authorisation is valid for three years and may be renewed. Renewals of the authorisation are valid for five years.
- Two products are authorised and available on the agency’s website.
- One of the approved products is a CAR-T. This seems the only approval for a CAR-T granted under HE in the EU.
- This CAR-T product ARI-0001 is also eligible for reimbursement by the Spanish national health care system.

5.7 Information on Additional countries

Some additional information on the HE in other EU countries is provided in the following table.

Table 2: Singular Information on additional countries

Country	Comments	Reference
Austria	The GMP inspectorate of the Federal Office for Safety in Health Care ("Bundesamt für Sicherheit im Gesundheitswesen", (BASG)) is responsible for issuing the HE in Austria. The Austrian Medicinal Products Law (AMG) provides a definition for the hospital exemption in §7 (6a and 6b) AMG. GMP for ATMPs should be applied. Generally, for application of ATMPs, the following is required. However, there is no monitoring or register of HE products: • Manufacturing Authorisation according to § 63 AMG ("Betriebsbewilligung"), issued via the BASG. • Acceptance of the ethical committee of the hospital where the administration/treatment (new method) should take place. • Authorisations according to GSG (Gewebesicherheitsgesetz), BSG (Blutsicherheitsgesetz), GTG (Gentechnikgesetz) (laws relating to tissues, cells, blood and genetically modified organisms). The requirements of AMG §7 (6b) applies for Pharmacovigilance (see section 5.7.1). Traceability of tissues is according to §§ 5 paragraph 4 and 16 paragraph 5 of the Tissue Safety Act (GSG), as well as the Reporting obligations according to §§ 17 and 32 of the Tissue Safety Act (GSG) with regards to cells and tissues. There is also a detailed guidance on the use of unauthorised ATMPs in hospitals (Hospital Exemption) in Austria on the internet. However, this guidance is not valid any longer. There do not seem to be any HEs approved at least until 2018. The whole procedure is under revision.	Ö-AMG „Leitfaden zur Anwendung von nicht zugelassenen ATMPs in Krankenanstalten (Hospital Exemption) in Österreich" Coppens et al. 2020
Belgium	Due to stringent provisions and long timelines and difficulties of facilities to be GMP compliant, manufacturers appear not to apply for HE.	(Coppens et al. 2020)

Italy	The legal basis is provided in The Medicinal law (Decreto 16 gennaio 2015) Authorisation to use ATMPs on a non-repetitive basis can be submitted for all ATMPs. A manufacturing license and GMP compliance is also required. Additional documentation is required for gene therapy products (see DTMA below). The Authorisation Holder can be a company or public institution. The application for ATMP approval requires a Dossier ("DTMA"), including a description and rationale of the manufacturing process, positive risk/benefit assessment, proposed treatment protocol and SmPC. A more detailed description of DTMA can be found on the webpage in the document "Istanza di autorizzazione alla produzione di medicinali per terapie avanzate su base non ripetitiva" (Application for authorisation to use ATMP on a non-repetitive basis). The form for application of the manufacturing license is provided on the same site. According to Coppens et al. 2020, two HE products have been manufactured in public facilities. No details are provided but according to Coppens these are not GTMPs. It is notable that five ATMP products have been manufactured in public facilities under "named patient use" outside of the HE framework between 2015 and 2017. Facilities reported that short timelines for approval facilitated use of exemption pathways.	https://www.aifa.gov.it/en/uso-non-ripetitivo-di-terapie-avanzate (Coppens et al. 2020)
Lithuania	On 28 July 2010 the Minister of Health of Lithuania approved special rules on manufacture of advanced therapy medicinal products for individual patients, which includes requirements for quality, safety, traceability and pharmacovigilance. The competent authority, which is responsible for authorisation of exempted ATMP in Lithuania is the State Medicines Control Agency of Lithuania. National Law was supplemented. "Non-routine basis" is defined as preparation when the modified manufacturing processes are applied for every medicinal product or when the frequency may not be attributed to routine manufacture. Manufacture of ATMP must be carried out in accordance with GMP and related to EU institutions documents to the extent that they can be applied. Practically, the GMP rules may be applied not in the full scope and some exemptions may take place. The prescription and the use of ATMP under the hospital exemption must take place in the same hospital. Until 2017 no permissions were granted.	(Ivaskiene, Mauricas, and Ivaska 2017)

Poland	Poland incorporated Article 28 of Regulation 1394/2007 into the Polish Pharmaceutical Law. On 29 June 2011 Minister of Health of Poland adopted the regulation, which confirmed the application form with requirements for an authorisation to the production of advanced therapy medicinal products. On 12 April 2013 Main Pharmaceutical Inspector and Director of the National Center for Tissue and Cell Banking approved Bulletin No. 1/2013 on the rules for obtaining approval for the production of advanced therapy medicinal products. The competent Authority in Poland, which is responsible for hospital exemption applications is the Main Pharmaceutical Inspectorate. “Non-routine”: ATMP must be prepared on “unsystematic” basis. Based on the information given it is not clear if the licence would be limited in time. Manufacture must be under GMP. There are no requirements concerning the prescription and use in the same hospital or manufacture in the same hospital. 2017: eight permissions were granted	(Ivaskiene, Mauricas, and Ivaska 2017)

6 Overall summary and Conclusion

6.1 Summary

- Usually, the Competent Authority for marketing authorisation of medicinal products is responsible for issuing a HE (e. g. DE, ES, UK, SE) which ensures that similar standards can be requested and enforced where applicable.
- There are two approaches:
  1. Product-specific approvals are issued in DE, ES, NL and SE based on manufacturing licenses. This allows for more nuanced and individual control at the product level but requires good oversight in order to be consistent between different products.
  2. HE manufacturing licenses for establishments are issued rather than individual products (FR, UK); labelling and product information is still required. This option is less burdensome to authorities and gives more freedom to manufacturers; however, it is therefore also more difficult to control.

- An initial HE approval is usually restricted in time (3-5 years).
- A HE approval can be modified and renewed.
- Definition of “non-routine”:
  - DE and UK describe their own approach.
  - A concrete number of administrations to patients or batches produced per year are usually not provided or published. The likely reason is that this depends on the prevalence of the indication treated, the difficulty of manufacturing and other factors, and a hard cut-off may put the authority in a difficult decision where this threshold is crossed in a particular year while the product otherwise clearly qualifies for “highly individualized treatment”.

- Documentation:
  - A CTD-like documentation is required for submission in DE, ES and FR (adapted format). This may make it easier for the authority to review and also provide a useful guide for the applicant so that no important information is omitted; however, it may increase the administrative burden and efforts for applicants.
  - Some other countries request comprehensive information with the application form (e.g. NL).

- Annual reports are mostly requested. This usually must include the number of batches/information about the frequency of use and PV reporting.
- Type of ATMPs:
  - No type excluded
  - However, mostly approved for HE: TEP and SCTMP
  - Gene therapies approved in FR (HE trials) and ES (CAR-T)

- Product database available for DE, ES
- Manufacturing license database available for FR, UK

- HE Authorisations are issued to:
  - Only hospitals / non-profit organisations: ES
  - Hospitals and companies: DE (needs to be a pharmaceutical entrepreneur), NL (to be a legal entity that is responsible for the production of the ATMP concerned), FR (but only hospitals use it), SE, UK
- (Preliminary) clinical data are sometimes required: in DE and ES; in most other countries supportive on a case-by-case basis (FR, NL, SE)
- All MS are applying the HE in parallel to clinical trials (indications can be overlapping, mostly no information is available)
- As the nationally approved ATMPs must generally meet the same specific quality standards that apply at the European level to centrally authorised ATMPs, production must take place under Good Manufacturing Practice. However, the GMP levels applied by inspectors may vary depending on stage of development. The relevant overarching GMP guidance applied is "GMP for ATMPs". This includes requirement for a QP (exception UK).
- RMPs are usually requested: DE, NL, FR, SE. AEMPS (ES) can request the RMP any time. For UK it needs to be prepared based on prior risk-assessment.
- The ATMP Regulation lays out that the same rules for traceability and pharmacovigilance apply for HE as for the centralised MA. Differences between MS might arise in the details of how reporting is expected, format of reports and required data:
  - QPPV or similar national PV person
  - PV-System
  - Traceability acc. to "GMP for ATMPs".

Table 3: Overview of countries applying the HE as product approval or based on manufacturing license only, countries that do not seem to apply HE or where it is not known. The provided data is partly from own research, partly from the publication of Eder und Wild 2019 (*) or Coppens et al. 2020 (**).

Countries that apply HE (No. of approvals in brackets)	Countries not applying HE	Not known
Czech Republic*[1]	UK	Romania*
France (8 establishments see 5.2.3)	Austria	Slovakia*
Germany (9, see 5.1.3)	Belgium*	Bulgaria*
Ireland*[2]	Lithuania*	Croatia*
Lithuania*[3]	Estonia*	Cyprus*
Netherlands (6, see chapter 5.3.3)	Finland*	Denmark*
Norway [4]**	Hungary*	Greece*
Poland (8, see chapter 5.7)	Iceland*	Liechtenstein*
Spain (2, see chapter 5.6.3)	Latvia*	Luxemburg*
Italy (2**, see chapter 5.7)	Portugal*	Malta*
Sweden (Number unknown*[5], see chapter 5.5.3)		Slovenia*

* Eder und Wild 2019, HE numbers from 2017

** Coppens et al. 2020, HE numbers between 2009 and 2017

1 Chondrocytes

2 Limbal stem cells

3 Dendritic cells, cytokine activated killer cells, T-cells, stromal vascular fraction cells

4 Chondrocytes, autologous T-cells, autologous dendritic cells, skin cells

5 Chondrocytes, mesenchymal stem and stromal cells, fetal stem cells and keratinocytes

6.2 Individual solutions

6.2.1 AUTHORITIES INVOLVED

- In some countries HE are issued via other Authorities than the NCA:

NL: Ministry responsible for Hospital exemption approvals is the Healthcare and Youth Inspectorate (Inspectie Gezondheidszorg en Jeugd, IGJ), not the MEB

- In some cases additional authorities or committees are involved:

FR: Agence de la biomédecine provides a scientific opinion as expert committee.

ES: Spanish Committee for Advanced Therapies

- Approval by the hospitals' ethical committees seems to be required in ES, AT (?) and FR.

6.2.2 TRANSITION PERIOD

- Some countries (like DE and ES) defined an additional transition period for products applicable for HE that had been on the market before the ATMP regulation came into force. This meant that applicants could apply for HE via an abbreviated application during that transitional time. The whole HE dossier would be submitted at a later date defined by the Authority. The product would still be allowed to be administered up to the point of the authorities' decision. These transition periods ceased at the latest in 2015. Examples:

  ES: chondrocytes, the implantation of keratinocytes for the treatment of burns or the treatment of corneal lesions with limbocorneal stem cells

  DE: chondrocytes, implantation of keratinocytes for the treatment of burns.

6.2.3 GMP/MANUFACTURING

- UK does not require a formal QP
- No product specific approvals but approvals based on Manufacturing licenses for product classes (FR, UK) are issued.

6.2.4 DATA BASE

- A transparent data base for product including SmPCs is available for: DE, ES
- A data base for manufacturing licenses for establishments rather than products are available:

  FR: MTI-PP license per establishment including the approved product classes and if these are used as single HE or as HE within a clinical trial. Specific details regarding the applications have been analysed and summarised in a poster (2019) on the ANSM's website

  UK: MeAT licenses would be included in the existing database for "register of licensed manufacturing sites" if there would have been a license
- A stakeholder may apply for a clinical trial under the hospital exemption regulation in France.

6.2.5 STATUS OF HE

- HE "in use": DE (9 Products), ES (2 products), FR (8 establishments), NL (6 products, but not used lately), SE (Number unknown), Italy (2 products in 2020) Poland (8 in 2017)
- No or almost no HE: UK (0), AT (0), Lithuania (0 in 2017)
- Treatment with Gene Therapies is currently possible in: FR (HE within clinical trials), ES
  Only in ES is there a specific a CAR-T product approved.
- UK is making use of their "specials" scheme instead of the HE. A more "marketing authorisation type" of early access option for patients with life threatening or seriously debilitating conditions is authorisation according to early access to medicines scheme (EAMS).

6.3 Open issues around HE

- Products that received a centralised MA might have to compete with HE approvals in the same or similar treatment areas.
- A recent position paper by EuropaBio summarizes industry's concerns and may be a useful guide to BAG on what pitfalls to avoid. EuropaBio is summarising most critical topics also from industry perspective, mentioning:
  - Inconsistent interpretation, EuropaBio requested a consistent harmonized interpretation of non-routine use and meaning of "within the same Member State"; Quality and PV Standards as well as GMP standards that are applied to be equivalent to those for authorised ATMPs.
  - HE should only be applied in the absence of centrally authorized products. The European Commission should work with National Competent Authorities to ensure that the HE is not being used by developers of ATMPs as an alternative to the centralised approval pathway as set out in the ATMP Regulation.
  - Transparency how HEs are used, EuropaBio proposes a Register for HE products to capture and provide information on safety and efficacy. They also propose a harmonised EU Informed Consent Form.
- In Germany: The approval according to §4b (3) AMG is required when the product is dispensed to other parties ("Abgabe an Andere"). If no dispensing takes place (e.g. in the same department of a hospital) only the manufacturing license is required. This implies that authorities might not be able to detect all establishments that manufacture and sell unauthorised products without notification to the authority.
- The problem of unauthorised cell therapies is also pointed out by EMA: https://www.ema.europa.eu/en/documents/public-statement/ema-warns-against-using-unproven-cell-based-therapies_en.pdf
- An additional example for not using existing HE schemes is reported for Belgium (Coppens et al. 2020) where manufacturers criticise that due to stringent provisions, long timelines and difficulties to reach GMP compliance manufacturers do not apply for HE. On the other hand, in the same publication it is reported that short timelines for HE application procedures in Italy and the Netherlands facilitated manufacture under HE.
- The hospital exemption shall focus on the national use and administration of ATMPs within one MS. Import and export of HE products should not take place, discouraging commercialisation of such products between different countries. On the other hand, important access to patients in

need of a certain therapy might not be covered in the one MS. This may be a reason why applicants use the "Specials" scheme in the UK. They have the possibility to administer their product elsewhere or import what their patients need. On the other side, FR included by-law that their HE products could be imported and exported.

- Reimbursement is a topic of vital importance for all ATMPs and this is even more difficult for exempted ATMPs as they are often considered as "unauthorised" medicinal products. Generally, reimbursement is possible in various countries, but this is highly variable between, and even within countries, and product types: more information can be part of a detailed additional analysis.

6.4 Conclusion

Based on the detailed analysis of six MS (DE, NL, FR, SE, ES, AT) and the UK as well as three additional MS (IT, LT, PL) with less systematic analysis it can be concluded that the major features of the HE as stipulated in relevant EU legislation and as outlined in the introduction are followed (PV, Traceability, GMP for ATMPs).

There are differences in the individual details required for a HE approval. Some countries require extensive documentation and authorise specific products while others authorise establishments based on manufacturing licenses for ATMP product types.

Several MS make use of the HE but it is also apparent that quite a few MS do not use the HE at all or have not used it in the past few years.

All MS are applying the HE in parallel to clinical trials with some countries requiring clinical trial data as a prerequisite for HE applications and others with a more risk-based approach and less control of efficacy (especially with the "only manufacturing license" approaches).

Controversies are related to HE products competing with centrally authorised products as well as to very different approaches concerning the definition of "prepared on a non-routine basis". Some countries open the HE to companies during their product development, other countries restrict HE to products to be applied in low numbers to patients with high-medical need in life threatening conditions.

Finally, it also has to be considered how to restrict the business and distribution of uncontrolled and even illegal cell therapies.

There is no "one size fits all solution" and the question always is what a regulation should achieve and which patients and applicants it should reach.

7 Recommendation

Generally, it is recommended designing an approach based on §28 (2) of the EU ATMP regulation for a Hospital exemption clause. For such an approach, it is recommended making clear-cut restrictions

that on the one hand give sufficient flexibility to both the applicant and the authority (the latter is an important aspect), but on the other also allow to steer applications should they cross the line to become "industrial" or would, in the authority's view, better be regulated under the regular legal framework. Any advanced therapy medicinal product would only be eligible for Hospital Exemption if:

- it is prepared on a non-routine basis according to specific quality standards, and,
- as a default be used within the same Member State (MS) 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.

As provided in the report there are different approaches in the countries, and the legislators and regulators put different emphasis on certain aspects depending on the goal to be achieved. It is recommended tailoring the framework to the needs of the Swiss population, even if some aspects may deviate from the EU framework. A guiding principle could be a rationale as a starting-point, based on which the framework is then designed, for example "a flexible regulatory framework that provides cutting-edge products to Swiss patients, that is well-controlled and controllable by the authority, easy to manoeuvre for applicants, and gives sufficient reassurance to patients that products are of state-of-the-art quality, efficacious and safe – whilst not undermining regular product development and avoiding unfair competition". One can debate if this option should only be applied in cases of life-threatening and seriously debilitating diseases or if treatments should also be available to patients whose treatments are not satisfactory as, for example, in cases of shoulder, hip or intervertebral disc cartilage repair.

Further, the approach should enable the production of ATMPs notwithstanding if it might ever be developed to be marketed as medicinal product.

It is vital that the BAG / Swissmedic has measures in place to control the HE.

One can identify two opposite groups of products:

1. Products for high medical need, in life-threatening, seriously debilitating conditions
2. Products providing innovative therapies for early access to patients also in less life-threatening but in therapeutic areas with so far unsatisfactory treatment.

7.1 Recommended elements in each case

- **Mechanism in place to control the respective HE**

The agency should **be able to withdraw** an approval essentially at any time; for example

- when a product is approaching to be in "routine use" and better regulated by regular development and authorisation pathways.
- if a similar ATMP product in the same indication is regularly authorised and readily available (if not, for example for highly complex products where demand cannot be met to sufficient scale, there may still be a case for allowing the HE-authorised product to stay on the market). For example, in that case after a transition period the product which is

available via HE has to be withdrawn, or a new application with adapted indication is required (see Spherox/Chondrosphere case in Germany).
- if a company is not willing to perform clinical trials, if a company generally ceased to proceed with clinical development towards clinical trials.

An **annual report** is a very efficient tool for control, including quality information (like batch analysis data), number of patients treated, safety reporting (as in PSUR) but also some key information on efficacy after one year, if feasible.
The HE should always be restricted to a certain time and the Agency needs to be informed about significant changes. The nature of these changes should be clarified in the guidance/law.
HE in parallel to clinical trials / clinical development but without jeopardising the conduct of clinical trials (which should be encouraged as clear preference) with a requirement to collect data on efficacy and safety can be considered, especially where the indication studied is not the one covered by HE.
Measures should be in place that prevent applicants circumventing clinical trials for situations where clinical trials would in principle be possible.

- **Quality of product:**

It should not make a difference to patients if they receive a HE product, an investigational product in clinical trial or a regularly approved product. Quality should not be debatable.
Therefore, GMP has to be in place, GMP for ATMPs has to be applied (case-by-case depending on stage of product and risk) and a proper description of manufacturing and controls as they are in an IMPD or module 3 provided.
It is recommended to consider how changes to manufacturing should be handled. Ideally, any change to manufacturing should be reported to the Agency and be assessed; however, this may increase burden to manufacturers where manufacturing is “non-routine”.

- **Safety of the product**

PV (annual reporting, use of existing (S)AE reporting structure, responsible person for PV).
RMP: to define risk and apply risk-minimisation measures but the format should be adapted for hospitals to not increase administrative burden.
Establish traceability for final products and use existing systems for starting materials (tissue and blood coding).

- **Efficacy and Safety:**

Minimal efficacy information in the annual report.
Benefit-risk should be adequately documented and be confirmed by the Hospital Exemption holder in their annual report.

- **Import / Export of final ATMP**

While it should not be the default, it may be desirable to have a process in place that allows the import of an ATMP from one EU state to Switzerland for especially life-threatening / seriously debilitating diseases and in cases where no alternative treatment exists for individual patients. To enable multiple (but still non-routine) use, the responsible physician / hospital could apply for a HE approval providing a certain amount of data reasonably enabling for an estimation that the treatment can be expected to work and be safe (to be administered to patients in CH).

It might be interesting to be open for export of HEs in case a hospital in another country is in need of this product and there is no other authorised ATMP.
However, rules, controls and restrictions need to be in place restricting trade of such products in order to avoid circumventing the usual clinical development and approval processes.

- **Import of starting materials:**

Allowing the donation of starting materials (blood, tissue) from outside of CH can increase the treatment options for patients (in case of allogeneic products) when it is difficult to find donors within CH. Risk of trading this starting material should be considered.

- **Transparent database** with SmPC and a patient information leaflet is recommended in order to provide for adequate information to physicians and patients.

- **Responsibility**

In the EU definition of the HE, the treating, prescribing physician is responsible for the treatment. The question is if the prescribing physician should indeed be responsible or the manufacturer. The doctor may not be able to take responsibility for all aspects, especially manufacture of the product. A recommendation could be that it is both the prescriber "wanting" the product and the manufacturer. This would need to be a matter of a contractual agreement. At least CH should take this question and the legal implications into account.

7.1.1 ADDITIONAL CONSIDERATIONS FOR PRODUCTS FOR HIGH MEDICAL NEED, IN LIFE-THREATENING, SERIOUSLY DEBILITATING CONDITIONS (GROUP 1)

a. Apply during early clinical development (Compassionate use programs might be available for late clinical development).
b. Low numbers of production batches and applications per year, but apply no limit, decision on a case-by-case basis. Applicants may be required to justify that their product is still “non-routine” when submitting their annual report (see above under general).
c. Hospitals, non-profit organisations (like Red Cross) should be able to apply; if small biotech companies should be included is again a matter of debate but should not be excluded in order to allow for sufficient flexibility. An application form may contain a section on justification on why a particular product should be accepted as HE, allowing for the Agency’s scrutiny.
d. Manufacturers can be different from the applicant (if applicant is a hospital without a GMP facility but with a convincing concept, no GMP facility needs to be built).
e. Ideally establishment of a transparent process that is relatively easy and fast with striking the balance between an as low as possible administrative burden against certain quality standards to be in place.
f. In this respect, stakeholders may during the process request the authority to publish “general minimum standards” which would make it easier for them to comply. However, this is likely difficult since a wide variety of different products could be envisaged. It would not be unreasonable for the authority to deny such requests and rather point to general principles as outlined in this report and apply a case-by-case approach.

g. Basic clinical evidence where possible and feasible (case-by-case, ideally at least first-in-human or case studies; the authority will have to check if the legal framework outside HE would at all allow the generation of such data). The data provided should provide a reasonable likelihood that the product in question will be efficacious and safe in patients. This will prevent, for example, use of stem cell-derived products for virtually any indication without clear scientific rationale or supporting data, as seen in some "stem cell tourism" cases.
h. Emphasis on high assumed benefit but possibly also higher risk due to missing data. Consider that these products might never aim for a MA. This is why applicants should be encouraged to steer their product into a regular development wherever possible. The authority will likely have incentives like early scientific advice in order to guide applicants into this direction.

7.1.2 ADDITIONAL CONSIDERATIONS FOR PRODUCTS PROVIDING INNOVATIVE THERAPIES FOR EARLY ACCESS TO PATIENTS ALSO IN LESS LIFE-THREATENING CONDITIONS BUT IN THERAPEUTIC AREAS WITH SO FAR UNSATISFACTORY TREATMENT (GROUP 2)

The considerations for Group 1, above, apply but additionally:

a. Generally, companies and hospitals can apply. It should be considered how late in the clinical development programme companies would be permitted to apply for the HE, such that they do not use the HE for competitive advantage. (This should be monitored, see Germany as case, compare with definition of "non-routine" is provided in §4b (2) AMG). Alternative provisions like Compassionate Use may be preferred routes, under the permission of the authority.
b. First clinical evidence should be considered mandatory in case of non life-threatening indications (to be assessed in application) with a discussion and justification by the applicant on the benefits and risks vis-à-vis current standard of care. Such advantage could be in efficacy, but also safety or pharmaceutical quality or any other patient benefit (e.g. easier to administer, less regular administration, etc.).
c. High emphasis on safety and efficacy and a positive benefit-risk ratio especially in non life-threatening indications.
d. HE might provide an additional incentive especially if the orphan drug legislation does not apply. This may require justification in the approval.

Every decision and approval of HE leads to the question of whether the treatment will be reimbursed despite often low evidence of clinical efficacy and usually missing comparison to standard therapies. A reimbursement has to be seen in conjunction with regularly authorised products that might compete with HE products. Therefore, the design of a HE clause would preferably include the payer's perspective as well.

We would recommend that once there is a draft of a Hospital Exemption regulation available, for the BAG to publish it for public consultation with stakeholders like Hospital, Companies, Patient organisations.

8 Acknowledgements

I want to thank Dr. Christian K. Schneider for his valuable input to the conclusions and recommendations chapter, review of the report, and many helpful discussions.

I also want to thank Dr. Martin Mewies for reviewing and editing the report.

9 References

co.don. 2019. 'Fachinformation: co.don chondrosphere® 10-70 Sphäroide/cm^2, matrixassoziierte Zellen zur Implantation', *Genehmigungsnummer PEI.A.11507.01.1*.

Coppens, D. G. M., Hoekman, J., De Bruin, M. L., Slaper-Cortenbach, I. C. M., Leufkens, H. G. M., Meij, P., and Gardarsdottir, H. 2020. 'Advanced therapy medicinal product manufacturing under the hospital exemption and other exemption pathways in seven European Union countries', *Cytotherapy*, 22: 592-600.

DRK BaWüHe. 2014. 'Fachinformation: Zytokin-aktivierte Killerzellen (CIK-Zellen), allogen, ≤ 1x108 CD3+CD56-T-Zellen/kg Körpergewicht in ≤ 100 ml Infusionsdispersion', *Genehmigungsnummer: PEI.A.11630.01.1*.

EC Pharmaceutical Committee. 2012. 'Hospital exemption for ATMPs (implementation of Art 28(2) of Regulation 1394/2007): update on feedback received by the Commission', *Agenda item 1. a) PHARM 608*.

Eder, C., and Wild, C. 2019. 'Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption', *J Mark Access Health Policy*, 7: 1600939.

Goula, A., Gkioka, V., Michalopoulos, E., Katsimpoulas, M., Noutsias, M., Sarri, E. F., Stavropoulos, C., and Kostakis, A. 2020. 'Advanced Therapy Medicinal Products Challenges and Perspectives in Regenerative Medicine', *J Clin Med Res*, 12: 780-86.

Ivaskiene, T., Mauricas, M., and Ivaska, J. 2017. 'Hospital Exemption for Advanced Therapy Medicinal Products: Issue in Application in the European Union Member States', *Curr Stem Cell Res Ther*, 12: 45-51.

medac. 2020. 'Produktinformation (Gebrauchs- und Fachinformation) Obnitix® „Humane allogene mesenchymale Stromazellen DRK-BaWü-He-FFM, expandiert, kryokonserviert“; 1-3x106 MSCs/ml in ≤ 50 ml Infusionsdispersion', *Genehmigungsnummer PEI.A.11748.01.1*.