REGULATORY REQUIREMENTS FOR CAR-T CELL THERAPY AGAINST CANCER

A COMPARISON BETWEEN THE EU AND THE US

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Dr. Ornella Fumagalli
aus Freiburg/Brsg.

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Betreuer und 1. Referent: Dr. Josef Hofer

Zweiter Referent: Dr. Bettina Klug

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List of Abbreviations

ADR	Adverse Drug Reaction
ALL	Acute Lymphoblastic Leukaemia
ATMP	Advanced Therapy Medicinal Product
BLA	Biologics License Application
CAR	Chimeric Antigen Receptor
CAT	Committee for Advanced Therapies
CBER	Centre for Biologics Evaluation and Research
CDER	Centre for Drug Evaluation and Research
CDRH	Centre for Devices and Radiological Health
CFR	Code of Federal Regulations
CGTP	Cell and Gene Therapy Product
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing & Control
CMO	Contract Manufacturing Organisation
COG	Cost of Goods
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
CR	Complete Remission
CRES	CAR-T Cell Related Encephalopathy Syndrome
CRi	Complete Remission with incomplete blood count recovery
CRS	Cytokine Release Syndrome
CTA	Clinical Trial Application
DFS	Disease-Free Survival
DLBCL	Diffuse Large B Cell Lymphoma
DSMB	Data and Safety Monitoring Board
e.g.	Example given
EC	European Commission
EFS	Event-Free Survival
EMA	European Medicines Agency
EPAR	European Product Assessment Report
ERA	Environmental Risk Assessment
ETASU	Elements to Assure Safe Use

EU	European Union
FDA	Food and Drug Administration
FDCA	Food, Drug & Cosmetics Act
FIH	First in Human
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GTMP	Gene Therapy Medicinal Product
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ITF	Innovation Task Force
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MRD	Minimal Residual Disease
MSCV	Murine Stem Cell Virus
NOG	NOD/Shi-*scid*/IL-2Rγ^{null} mouse (severely immunodeficient)
OCTGT	Office for Cellular, Tissue and Gene Therapies
ORR	Overall Remission Rate
OS	Overall Survival
PFS	Progression-Free Survival
PHSA	Public Health Services Act
PIP	Paediatric Investigational Plan
PMR	Post-marketing Requirements
POC	Proof of Concept
PRIME	Priority Medicine
RBA	Risk-based Approach
RCL	Replication-competent Lentivirus
REMS	Risk Evaluation and Mitigation Strategy
RMAT	Regenerative Medicine Advanced Therapy
SA	Scientific Advice
SAWP	Scientific Advice Working Party
SBRA	Summary of Basis for Regulatory Action
SCT	Stem Cell Transplantation
sCTMPs	Somatic Cell Therapy Medicinal Product
SME	Small and Medium Enterprise

SNIF	Summary Notification Information Format
SPA	Special Protocol Assessment
TCR	T Cell Receptor
TLS	Tumour Lysis Syndrome
TPP	Target Product Profile
UK	United Kingdom
USA	United States of America

1 INTRODUCTION

For many decades cancer therapy consisted of surgery, chemotherapy and/or radiotherapy. CAR-T cell therapy is a relatively novel concept in the field of cancer therapy and has given a lot of hope to cancer patients and their families. The therapy is based on stimulating the patient's immune system and is designed to cure the disease: with a single treatment specific types of cancer can be healed [1].

Products belonging to this therapy group are classified as gene therapy medicinal products (GTMP), a subgroup of advanced therapy medicinal products (ATMPs) in the European Union (EU) [2]. In the United States (US) they belong to the regulatory group of regenerative medicine therapies, including cell and human gene therapy products [3].

The most promising subclass of GTMPs in the field of cellular cancer immunotherapy are chimeric antigen receptor (CAR) T cells. In 2018, the first two products, Kymriah® (Novartis) and Yescarta® (Kite Pharma/Gilead), obtained regulatory approval in the EU for treatment of acute lymphoblastic leukaemia (ALL) and diffuse large B-cell lymphoma (DLBCL), refractory to a standard chemotherapy regimen or relapsed after stem cell therapy (SCT). DLBCL is the most common subtype of Non-Hodgkin lymphoma [4].

The concept of CAR-T cells is based on the principle to teach the patient's immune system to recognise and eliminate cancer cells and is shown in Figure 1:

The ability of T cells to recognise specific antigens is defined by the T cell receptor (TCR). The extracellular part of the TCR recognises foreign molecules and activates the intracellular domain of the TCR to generate a signal. This signal can for example stimulate B cells to produce antibodies, direct neutrophils to eliminate microbes or it can induce T cell transformation into a cytotoxic T cell, which will directly kill the target cell [5].

For CAR-T therapy patient derived T cells are required. White blood cells are removed from the patents' blood via leukapheresis followed by T cell isolation. These cells are transfected with viral vectors including the relevant CAR genes leading to a stable integration of the CAR genes into the T cell's genome. Long-term expression of the CAR on the T cell's surface is thereby given.

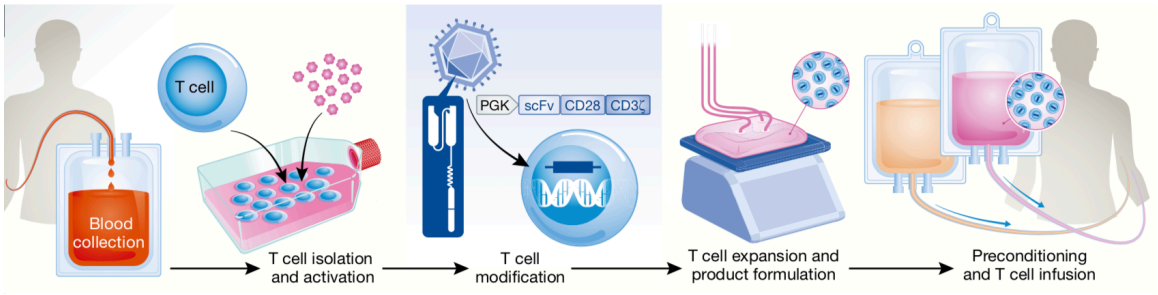

Figure 1: CAR-T cell therapy, source: Hartmann et al. [5].

The design of the chimeric antigen receptor is crucial for the success of the therapy. In general, a CAR is composed of three relevant domains, as shown in Figure 2: an extracellular binding domain, a transmembrane domain and an intracellular signal sequence. The extracellular binding domain is responsible for tumour recognition, consisting of an antibody fragment with a high tumour specificity. In the case of both Kymriah and Yescarta, the extracellular region corresponds to an antibody fragment specific for the B cell marker CD19, targeting B-cell cancers that overexpress CD19. The transmembrane domain provides the correct location and presentation of the CAR on the T cell's surface. Essential for T cell stimulation is the intracellular signal sequence transmitting a signal inside the cell, leading to tumour cell destruction. The combination of several signal sequences can enhance T cell activation and is subject to ongoing research [5].

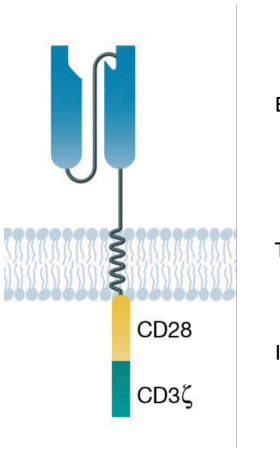

Figure 2: Schematic representation of a CAR displayed on the surface of a T cell, showing the extracellular binding domain, the transmembrane domain and the intracellular signal sequence. Source: Buchholz et al. [6].

Once T cells have been modified to include the CAR genes, they are activated and expanded before returning them to the patient intravenously, mimicking the natural progression of T cell development and generating a large number of functional CAR-T cells. Prior to receiving the modified T cells, the patient must be conditioned

by a lymphodepletion scheme to reduce the number of innate immune cells to optimise the condition for CAR-T cell expansion.
The CAR-T cells circulating in the patient's body recognise the tumour cells, convert to cytotoxic T cells and attack and destroy the tumour. In addition, binding to tumour cells induces proliferation of the CAR-T, which in fact is part of the uniqueness of CAR-T therapies as the active agent of the therapy replicates in the patient leading to a dose increase *in vivo*. After elimination of the tumour cells CAR-T cells persist in the patient and get reactivated when target tumour cells reappear in the patient.

In this master thesis the European and US regulatory environment and requirements for CAR-T cell therapy against cancer will be summarised (chapters 2 & 3) and the path to licensure of the two approved CAR-T cell therapies Kymriah and Yescarta analysed (chapter 4). Based on this, requirements and challenges for CAR-T therapy development will be evaluated and a potential regulatory strategy for the EU and the US proposed (chapter 5). A final assessment on which ICH region to choose for CAR-T therapy development – the EU or the US - will follow in chapter 6 and an outlook will be given in chapter 7.

2 European Regulatory Requirements for Cellular Immunotherapies

The legal basis for a marketing authorisation for ATMPs is given by Directive 2001/83/EC as amended by Commission Directive 2009/120/EC, Regulation 1394/2007 and Regulation 726/2004 [7,8,9,10]. For all products covered by the Annex to regulation 726/2004, the centralised procedure is mandatory. So the decentralised procedure, the mutual recognition procedure or a national procedure are in general not an option for ATMPs. The only exemption of this is the "hospital exemption", based on Article 28 of regulation 1394/2007. Under this exemption an ATMP is prepared in a hospital under the responsibility of a medical practitioner for an individual patient. In this case the manufacturing of the product must be authorised by the national competent authority.
In addition to the above mentioned directive and regulations several guidelines are relevant for cellular cancer therapy; see Table 1 for an overview.

Table 1: Overview of the EU Regulatory Framework for Cell Based Immunotherapy Against Cancer

Document	Effective since or status	Ref.
Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer	09/2016	11
Reflection paper on management of clinical risks deriving from insertional mutagenesis	04/2013	12
Guideline in follow-up of patients administered with gene therapy medicinal products	05/2010	13
Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products	11/2008	14
Reflection paper on design modifications of gene therapy medicinal products during development	12/2011	15
Guideline on human cell-based medicinal products	09/2008	16
Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products	11/2008	17
Guideline on the quality, non-clinical and clinical aspects of gene therapy medicinal products	03/2018	18
Guideline on safety and efficacy follow-up and risk management of advanced therapy medicinal products	Draft, end of consultation 04/2018	19
Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells	Consultation until 07/2019	20
Guideline on quality, non-clinical and clinical requirements for investigational advanced therapy medicinal products in clinical trials	Consultation until 08/2019	21
Guidelines on good manufacturing practice specific to advanced therapy medicinal products	05/2018	22
Consultation document, Good clinical practice for advanced therapy medicinal products	(2018)	23
Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to advanced therapy medicinal products	12/2013	24

2.1 Committee for Advanced Therapies

In accordance with regulation 1394/2007, a multidisciplinary committee was established at the European Medicines Agency's (EMA), the Committee for Advanced Therapies (CAT), which is responsible for the quality, safety and efficacy assessment of ATMPs. During the centralised procedure the CAT adopts the draft opinion, the Committee for Medicinal Products for Human Use (CHMP) adopts the final opinion which is passed on to the European Commission (EC) for final decision. For better exchange and collaboration between CAT and CHMP, five members are participating in both committees.

2.2 Classification of ATMPs

Besides of the evaluation of a marketing authorisation application (MAA), the CAT is also involved in the classification of ATMPs, to determine whether a medicine should be classified as ATMP and if so, under which category. It is a 60-day procedure, involving the consultation of the EC. The outcome of the assessment is published on the EMA website as summary reports [25].

2.3 Certification of Quality and Non-Quality Data

Another ATMP specific tool is the certification of quality and non-quality data for Small and Medium Enterprises (SME) [26]. It is based on a scientific evaluation of the submitted data, which is not binding for future MAAs or clinical trial applications. It represents a compliance check with Annex I to directive 2001/83/EC on scientific and technical requirements. A benefit/risk assessment is not part of the evaluation process. After a validation check, the procedure takes 90 days, resulting in an EMA certificate or refusal letter. The aim of the certificate is mainly to support SMEs in their out-licensing activities.

2.4 Scientific Advice and Consultation

Timely engagement with regulatory authorities is crucial for the development of innovative new medicines, as they are challenging in a scientific as well as regulatory manner. Developers can request scientific advice (SA) from the EMA at any stage of development. Several types of consultation are available [27]:

- Scientific advice focused on development strategies (prospective), based on specific questions posed by developer
- Protocol assistance, special form of scientific advice for developers of designated orphan medicines

- Parallel scientific advice with health-technology-assessment (HTA) bodies to obtain feedback from regulators and HTA bodies on their evidence-generation plans to support both marketing authorisation and reimbursement at the same time.
- Parallel scientific advice and protocol assistance with FDA

2.5 Innovation Task Force

The Innovation Task Force (ITF) is a forum for early dialogue between EMA and the applicants, in particular with SMEs to identify scientific, legal and regulatory issues of innovative therapies and technologies. Via ITF the applicants can also obtain advice on the eligibility to EMA procedures relating to research and development of the product [28].

2.6 Orphan Drug Status

Another very common characteristic of cellular immunotherapies is the orphan drug status [29]. Cellular immunotherapies are mostly being developed for the treatment of a life-threatening or chronically debilitating condition that is rare, meaning a prevalence of less than 5 in 10,000 people in the EU. If in addition to the prevalence criterion a few other criteria are met (see regulation 141/2000), an orphan designation application can be submitted to the EMA. The orphan designation provides valuable incentives such as fee reductions (especially for SME-sponsors) and market exclusivity of 10 years. Although the orphan designation is not specific for ATMPs and all types of medicinal products can request the orphan designation, from the six authorised GTMPs and sCTMPs in Europe, five are orphan drugs [30].

2.7 Regulatory Tools to Facilitate and Expedite Approval

For products and therapies that target an unmet medical need or address public health interests and are eligible for the centralised procedure, EMA offers several regulatory mechanisms to enable early patient access [31].

2.7.1 PRIME - PRIority MEdicine

In order to support the development of medicines that address an “unmet medical need” EMA has launched the PRIME scheme in 2016 [32]. It offers pharmaceutical developers an early interaction with the agency via scientific advices at key development milestones involving additional stakeholders such as health-technology-assessment to optimise development plans and the regulatory strategy. In addition, it enables accelerated assessment of the MAA so that

patients can benefit as early as possible from the new medicines. In order to be eligible for PRIME early clinical data showing potential benefit to patients are required. As of April 2019, 53 requests for PRIME eligibility for ATMPs have been submitted and 20 ATMPs have been granted access to the PRIME scheme [33].

2.7.2 Adaptive Pathways

As for PRIME it is a concept for medicinal development with the intention to shorten the time to access for patients in areas of high medical need, especially where it is difficult to collect sufficient data via traditional large trials [34,35]. It is based on iterative development which can be obtained through:

- an initial approval for a restricted patient population followed by an expansion of the indication (Type II variation) or
- a conditional approval based on surrogate endpoints followed by confirmation of the benefit-risk balance

Important features of this approach are data based on real-life evidence and early involvement of health technology assessment bodies. The regulatory processes involved are scientific advice, compassionate use and conditional approval in combination with collection of real-life data and a risk management plan.

2.7.3 Accelerated Assessment

The accelerated assessment procedure aims to reduce the review timeframe of a marketing authorisation application from the standard 210 days to 150 days (without clock stop) [36]. The legal basis is provided in Article 14(9) of Regulation (EC) 726/2004.

2.7.4 Conditional Marketing Authorisation

A conditional marketing authorisation may be granted before complete data are available, provided that the benefit-risk balance of the product is positive and the benefit of an immediate availability of the concerned product outweighs the risk due to need for further data. Conditional marketing authorisations are valid for one year and can be renewed every year. Specific post-marketing obligations must be completed to provide comprehensive data confirming the positive benefit-risk balance. Upon availability of the complete data package, the marketing authorisation may be converted into a standard marketing authorisation without specific obligations. The legal basis for a conditional marketing authorisation is given in Article 14(7) of Regulation (EC) 726/2004 and in Commission Regulation (EC) 507/2006 [37].

2.7.5 Marketing Authorisation under Exceptional Circumstances

A marketing authorisation under exceptional circumstances may be granted if comprehensive data on efficacy cannot be shown [38]. This can be due to low prevalence of the indication, lack of scientific knowledge or ethical reasons. The approval is subject to specific obligations within a time period which form the basis of the annual reassessment of the benefit-risk profile. A marketing authorisation under exceptional circumstances will normally not lead to the completion of a full dossier. The legal basis is stated in Article 14(8) of Regulation (EC) 726/2004 and Directive 2001/83/EC Annex 1.

3 US Requirements for cellular Immunotherapies

The Food and Drug Administration (FDA) is the federal regulatory agency within the Department of Health and Human Services of the US, responsible for authorisation of clinical trials and marketing approval for medicinal products. Within the agency three separate centres are responsible for medicinal products, biologic products and devices [39,40]:

- *Centre for Drug Evaluation and Research (CDER):* responsible for chemical-based drugs and some biotechnology products, including monoclonal antibodies and cytokines
- *Centre for Biologics Evaluation and Research (CBER):* regulation of biological and related products including blood, vaccines, allergenics, tissues, and cellular and gene therapies
- *Centre for Devices and Radiological Health (CDRH):* regulates medical devices and radiation emitting products.

Within CBER the Office for Cellular, Tissue and Gene Therapies (OCTGT) is responsible for Gene- and Cell-based Therapies.

The US regulatory framework is based on

- *Statutes* passed by the Congress and signed into law by the President
- *Regulations* implemented by the FDA, giving details on interpretation of laws
- *Guidelines* reflecting FDA interpretation to regulatory requirements, providing support on compliance for developers and FDA staff.

Two statutes authorize the FDA to regulate human medicinal products as drugs, biologic products or devices, the Public Health Services Act (PHSA) and the Food, Drug & Cosmetics Act (FDCA) [41,42].

Title 21 of the Code of Federal Regulations (CFR) specifies how FDA carries out the activities defined in PHSA and FDCA [43].

Guidelines can focus on particular regulatory topics, indication or product types. They are, however, not legally binding and alternative approaches are allowed if they comply with the FDA requirements.

The most relevant guidelines for cellular immunotherapy against cancer are given in Table 2.

Table 2: Overview of the US Regulatory Framework for Cell Based Immunotherapy Against Cancer

Document	Effective since	Ref.
Expedited programs for regenerative medicine therapies for serious conditions; Guidance for industry	02/2019	44
Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs); Draft guidance for industry	07/2018	45
Long Term Follow-up After Administration of Human Gene Therapy Products; Draft Guidance for Industry	07/2018	46
Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up; Draft Guidance for Industry	07/2018	47
Human Gene Therapy for Rare Diseases; Draft Guidance for Industry	07/2018	48
Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products; Guidance for Industry	06/2015	49
Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products; Guidance for Industry	03/2015	50
Preclinical Assessment of Investigational Cellular and Gene Therapy Products; Guidance for Industry	11/2013	51

3.1 Consultation Meetings for Scientific Advice

Developers can seek advice at the FDA related to the development of new drugs at critical points in the development process. There are three types of formal

meetings that occur between requesters and FDA staff: Type A, Type B and Type C [52,53].

Type A meetings are those necessary for a stalled product development programme to proceed or to address an important safety issue, e.g. a meeting to discuss a clinical hold.

Type B meetings are Pre-Investigational New Drug (IND) meetings, End-of-Phase 1 and Phase 2 meetings, pre-Phase 3 meetings and Pre-BLA meetings. Meetings regarding risk evaluation and mitigation strategies or post-marketing requirements are also considered Type B meetings, as well as meetings held to discuss the overall development programme for products granted breakthrough therapy designation status.

A Type C meeting is any meeting other than a Type A or Type B meeting regarding the development and review of a product, including meetings on the use of a biomarker as a new surrogate endpoint.

A *special protocol assessment* can also be requested to reach agreement with FDA on the design of clinical trials or animal studies to support marketing approval [54]. Aim of the special protocol assessment is to obtain written agreement about critical aspects of trial design and an FDA commitment to accept the study results for filing.

In addition to the above mentioned consultation possibilities, for CBER regulated products an additional type of meeting has been established: the **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s (INTERACT). The INTERACT meeting gives a developer the opportunity to obtain preliminary informal consultation with CBER art an early stage of development prior to a pre-IND meeting, previously known as pre-pre-IND meeting [55].

3.2 Orphan Designation

The orphan drug designation can be requested by developers for products with the potential to diagnose, treat or prevent a rare disease of condition that either affects less than 200,000 individuals in the US or if it is improbable that costs of research and development can be recovered by sales [56].

Orphan designation qualifies the developer of the drug for various incentives, including tax credits for qualified clinical testing. A marketing application for a prescription drug product that has received orphan designation is not subject to a

prescription drug user fee. In addition, 7 year of market exclusivity for approved orphan products are also granted.

3.3 Tools to Expedite Approval

Medicinal products that have the potential to treat serious conditions, particularly in patients with unmet medical needs are classified as Regenerative Medicine Advanced Therapy (RMAT) in the US, including cell therapy and human gene therapy [44]. FDA has established several programs to support the development of such therapies and to ensure the availability to patients with serious conditions as fast as possible:

- Fast Track designation
- Breakthrough therapy designation
- RMAT designation
- Accelerated approval
- Priority review designation

As with other biological products, regenerative medicine therapies receiving Fast Track designation, breakthrough therapy designation and RMAT designation must meet the standards for approval, including demonstrating effectiveness. A product might receive more than one designation, but separated requests are required.

3.3.1 Fast Track Designation

Fast Track designation's aim is to facilitate development and expedite review of an investigational new drug. Nonclinical or clinical data are required to demonstrate the potential to address an unmet medical need [57]. Fast Track designation must be requested by the drug company and can be initiated at any time during development. Once Fast Track designation has been received, frequent communication between FDA and the developer is encouraged either in form of meetings or written communication to assure that questions and issues on e.g. drug development plans or collection of appropriate data to support drug approval are resolved quickly. Ideally this should lead to earlier drug approval and access to patients.

In addition to the Fast Track designation an IND is also eligible for Rolling Review, Accelerated Approval and Priority Review, if applicable.

3.3.2 Breakthrough Therapy Designation

An IND is eligible for Breakthrough Therapy designation, if preliminary clinical evidence from Phase I or Phase II trials indicates that substantial improvement over available therapies on one or more clinically significant endpoints may be demonstrated [58]. All benefits of the Fast Track designation apply also for the Breakthrough Therapy designation. In addition, FDA guidance on efficient drug development and commitment to involve senior FDA staff are also advantages of this designation.

It is important to highlight, that the level of required evidence for Breakthrough Therapy designation is higher than for Fast Track designation. “Fast Track designation requires only that nonclinical or clinical data demonstrate the potential to address an unmet medical need, whereas for breakthrough therapy designation, preliminary clinical evidence must indicate that the product may demonstrate a substantial improvement over existing therapies” [44].

3.3.3 RMAT Designation

In March 2017 FDA introduced the new RMAT designation, highlighting the need for efficient regulatory tools to accelerate the development and commercial availability of regenerative medicines [44]. A drug is eligible for this designation, if it is

- a regenerative medicine therapy: cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products
- intended to treat, modify, reverse or cure a serious or life-threatening disease or condition and
- indicated by preliminary clinical evidence that it has the potential to address unmet medical needs.

The RMAT designation entitles to all the benefits of the Fast Track and breakthrough therapy designation programs, including early interactions with FDA especially to discuss potential surrogate or intermediate endpoints to support accelerated approval. Regarding demonstration of preliminary clinical evidence a certain degree of flexibility is accepted. Clinical investigations at the initial stage of product development may not always be prospective clinical trials with a concurrent control, but a historical control instead. Sometimes, clinical case series or data from well-designed retrospective studies are also acceptable as preliminary clinical evidence. However, it is essential that the preliminary clinical evidence is

generated using the product that the developer intends to use for clinical development.

In contrast to Breakthrough Therapy designation, it is not required to indicate that the drug may offer a substantial improvement over available therapies to be eligible for RMAT designation.

3.3.4 Priority Review Designation

Priority Review consists of a shorter period of evaluation of the biologics license application (BLA) by FDA/CBER reducing the review time from 10 months standard review to 6 months [59]. A product may be eligible for Priority Review, if it treats a serious condition and would provide a significant improvement in safety or effectiveness. At the pre-BLA meeting with CBER potential eligibility for priority review should be discussed. FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA. Designation of a drug as such does not change the requirements for approval or the quality of evidence necessary. Priority Review designation can be granted to products that received Fast Track, Breakthrough Therapy, or RMAT designation.

3.3.5 Accelerated Approval

Accelerated Approval may be granted to drugs in cases in which the disease course is long and an extended period of time would be required to measure the intended clinical benefit [60]. If a surrogate endpoint can be defined that is reasonably likely to predict clinical benefit or a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, FDA may grant accelerated approval based on these. Post-approval confirmatory studies are required to verify and describe the anticipated effects of the products on irreversible morbidity and mortality or other clinical benefit. Approval of a drug may be withdrawn or the labelled indication of the drug changed if trials fail to verify clinical benefit.

Accelerated approval should be discussed with FDA/CBER early in development to discuss proposed surrogate or intermediate clinical endpoints, plans to collect data obtained from a meaningful number of study sites, other clinical trial design issues and any considerations related to product quality and manufacturing.

4 Drug Development of Approved CAR-T Cell Therapies

In 2017, the first two CAR-T therapies have been approved in the US, KYMRIAH from Novartis and YESCARTA from Kite Pharma. The European approval followed in 2018 for both products.

Many CAR-T based products are currently under clinical evaluation. There are currently nearly 800 clinical trials ongoing involving CAR-T cell therapy [61]. An overview is shown in Figure 3.

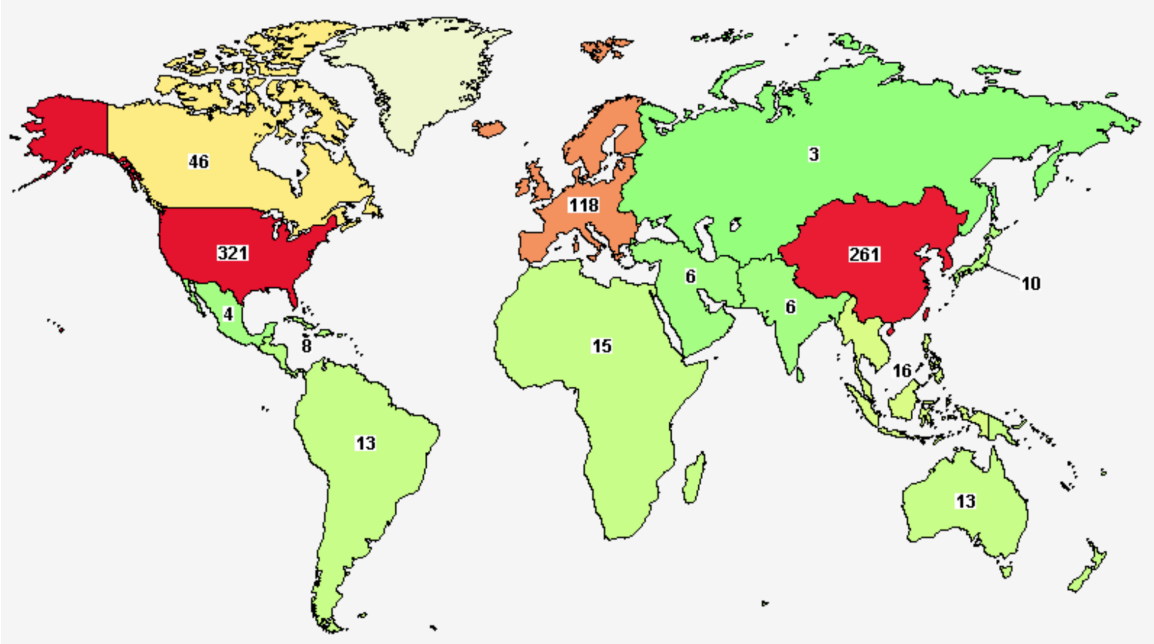

Figure 3: Overview of clinical trials involving CAR-T products worldwide, source: clinicaltrials.gov, April 2019 [61].

In the following chapters the development paths of both Kymriah and Yescarta will be summarised. In addition, challenges encountered during the review process of the agencies will also be specified.

4.1 Path to License for Kymriah

Kymriah (tisagenlecleucel) is an autologous T cell immunotherapy indicated for the treatment of

- Paediatric and young adult patients up to 25 years of age with B-cell acute lymphoblastic leukaemia (ALL) that is refractory, in relapse post-transplant or in second or later relapse.
- Adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy.

All information are taken from the "Summary of Basis for Regulatory Action" (SBRA) of the FDA [62,63] and the "European Product Assessment Report" (EPAR) of the CHMP/EMA [64].

4.1.1 Chemistry, Manufacturing and Control (CMC)

A patient's own T cells are genetically modified with a lentivirus to express a chimeric antigen receptor to identify and eliminate CD19 expressing cell, such as tumour cells.

The manufacturing process starts with collecting the patient's blood cells via leukapheresis. After enrichment and stimulation, T cells are transduced with a lentivirus vector encoding the relevant CAR genes. CAR expressing T cells are expanded, washed and formulated with infusion media for cryopreservation. Upon request, Kymriah is shipped in a vapor-phase liquid nitrogen dry shipper to the clinical infusion centre and infused back into the patient.

Throughout all steps of the whole process from leukapheresis to infusion a computer based chain-of-identity system ensures product's identity and traceability.

FDA Concerns on CMC

- *Manufacturing failure* would have a direct impact on patients. As Kymriah manufacturing has only experience an approximately 9% failure rate, this can be considered a minor issue.
- Generation of *replication-competent lentivirus* (RCL) during the manufacturing process is a theoretical safety issue. So far no RCL has been detected in any clinical trial using a cell product transduced by a lentivirus.
- *Insertional mutagenesis* due to integration of vector can potentially induce secondary malignancies by inadvertently activating cellular proto-oncogenes or disrupting tumour suppressor genes. Risk mitigation was addressed through vector design ("self-inactivating design") and a limited copy number per cell.

After pre-license inspections (PLI) at Novartis, as well as at the contract manufacturing organisations (CMO) for lentiviral vector manufacturing and at the CMO for sterilisation, concentration and filling of the lentiviral vector, FDA issued a Form 483 for each site. All three companies responded to the observations and the corrective actions were reviewed and deemed acceptable.

CAT/EMA Concerns on CMC

- Lack of appropriate documentation to demonstrate GMP compliance for the manufacturing/batch release sites was identified as a major objection. Novartis provided satisfactory documentation for all three sites and consequently the major objection was resolved.

Recommendations for future quality development included completing the characterisation and testing of the viral vector, the leukapheresis starting material and the finished product. Although proposed specifications were considered appropriate, Novartis should re-evaluate the release tests and their acceptance criteria based on post approval data.

4.1.2 Environmental Risk Assessment (ERA)

The magnitude of the following potential hazards and the evaluation of their likelihood has been assessed:

- Presence of RCLs in the final product and subsequent transmission of RCLs to thirds
- Formation of RCL in patients
- Transmission of replication-incompetent vectors
- Transmission of genetically modified T cells by accidental administration to thirds or after bleeding

FDA Concerns on ERA

A request for categorical exclusion from ERA has been accepted by FDA as manufacturing of Kymriah will not significantly alter the concentration and distribution of naturally occurring substances.

CMDH/EMA Concerns on ERA

Strategies to prevent risks for the environment are deemed as appropriate for the intended use of Kymriah.

4.1.3 Non-Clinical Pharmacology and Toxicology

Primary Pharmacology

The following primary pharmacodynamic studies have been conducted.

In vitro	• Selection of eukaryotic promotor expressing CAR against human CD19 • Selection of costimulatory domain for CD19-specific T cell function • CAR-T cell cytolytic activity against primary B-ALL tumour cells • Cytokine production of CAR-T cells after stimulation with tumour cells • Proliferation and survival of CAR-T cells without CD19 re-stimulation
In vivo	Mouse tumour model: • Determination of CAR-T specific tumour effects and dose optimisation • Determination of threshold of efficacy for CAR-T cells • Comparison of persistence, anti-B-ALL activity and effect on survival

No secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interactions studies have been conducted.

PHARMACOKINETICS

One non-clinical biodistribution study has been performed to investigate the pharmacokinetic properties of Kymriah in NOG mice engrafted with human acute B-ALL.

TOXICOLOGY

The non-clinical toxicology studies were not conducted in compliance with Good Laboratory Practice (GLP).

Genotoxicity was assessed by genomic insertion site analysis of lentiviral integration into the human genome of healthy donors and patients with B cell malignancies.

A toxicity study on impurities and excipients was performed to evaluate the potential for acute toxicity deriving from magnetic beads (Dynabeads) used for T cell enrichment and activation.

No toxicity studies have been performed regarding single dose, repeat dose, carcinogenicity, reproduction, toxicokinetic data or local tolerance.

In addition to the above mentioned studies, the following investigations have been performed:

- *In vivo* safety assessment of Kymriah in murine leukaemia xenograft model
- *In vitro* expansion profile studies of transduced T cells
- Evaluation of the specificity of the CD19-binding domain using a human plasma membrane protein array
- Immunohistochemistry, in situ hybridization and RT-PCR analysis on human and cynomolgus monkey tissues of the central nervous system.

FDA AND CAT/EU CONCERNS ON NON-CLINICAL DEVELOPMENT

The non-clinical documentation submitted was considered adequate.

4.1.4 CLINICAL DEVELOPMENT

To date Novartis has conducted four Phase II trials and has further planned two Phase I trials, five Phase II trials, including a long-term follow-up study and an expanded access study, and two Phase III trials [61].

The basis for the BLA and the MAA for the indication of ALL was provided by clinical trial B2202 (ELIANA, NCT02228096), an open-label, multicenter single-arm trial performed under Special Protocol Assessment.

The primary efficacy endpoint was overall remission rate (ORR), including complete remission (CR) and complete remission with incomplete blood count recovery (CRi). The ELIANA population for efficacy was 63 individuals; among these 83% achieved CR/CRi and all patients in CR were minimal residual disease (MRD) negative.

Regarding safety, 79% of the patients treated with Kymriah experienced cytokine release syndrome (CRS) and 65% of subjects had neurotoxicity. Hypogammaglobulinemia occurred in 43% of the patients. Two deaths were attributable to the product and considered by the FDA as related to CRS.

For the supplementary indication DLBCL, the clinical trial C2201 (JULIET, NCT02445248) was the basis for the supplementary BLA and the MAA. Efficacy assessment is based on 68 evaluable patients of the single-arm, open label, Phase 2 multicentre study. ORR was 50% and CR rate was 32%.

74% of the patients experienced CRS following Kymriah, neurotoxicity occurred in 58% of patients. Three patients deaths were partly attributed to CRS.

4.1.5 Post-Authorisation Obligations in the US

ALL indication: No efficacy concerns were mentioned by FDA. Regarding safety, a Risk Evaluation and Mitigation Strategy (REMS) including Elements to Assure Safe Use (ETASU) was requested. The REMS focuses on mitigating the known risks of cytokine release syndrome and neurotoxicity, and includes site certification and restriction of use to certain health care settings.

In addition as post-marketing requirement (PMR), a multicentre, prospective, observational safety study will include 1000 subjects enrolled within 3 months of the Kymriah infusion over 5 years, as proposed by Novartis. All enrolled subjects will be followed for 15 years from their Kymriah infusion. The primary endpoint will be evaluation for second malignancy.

DLBCL indication: The REMS for childhood B-ALL will be modified to include training information for the DLBCL indication.

The protocol for the PMR study proposed for ALL will be amended to include 1500 DLBCL patients who received Kymriah.

4.1.6 Post-Authorisation Obligations in the EU

ALL indication: To further evaluate the efficacy and safety of Kymriah in ALL patients below the age of 3 years, a post-authorisation efficacy study (PAES) study should be conducted and submitted based on data from a disease registry in ALL patients with a follow-up period of 20 years.

DLBCL indication: Three additional PAES studies were requested.

- PAES: a prospective, observational study in patients with DLBCL based on data from registry with efficacy outcome measures in line with study C2201, including details of the manufacturing turnaround time.
- PAES: 24 months follow-up for patients from study C2201 to further characterise long-term efficacy and safety of Kymriah. In addition the applicant should submit the final CSR including 5 years of follow-up.
- PAES: open-label, Phase III study of Kymriah versus standard of care in adult patients.

ALL & DLBCL indications: A non-interventional post-authorisation safety study (PASS) to assess safety and long-term safety should be conducted and submitted based on data from a disease registry in ALL and DLBCL patients (20 years follow-up).

4.2 Path to License for Yescarta

Yescarta (Axicabtagene ciloleucel) is an autologous T cell immunotherapy product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Relevant information is taken from the SBRA of the FDA [65] and the EPAR of the CHMP/EMA [66].

4.2.1 Chemistry, Manufacturing and Control

Yescarta is composed of autologous T cells transduced with a Murine Stem Cell Virus (MSCV) based retroviral vector containing a CAR directed against human CD 9. The manufacturing process comprises receipt of patient's leucocytes, enrichment and stimulation of T cells and transduction with the retrovial vector. CAR expressing T cells are expanded ex vivo, washed and formulated with infusion media for cryopreservation.

FDA Concerns on CMC

- *Loss of chain-of-custody (COC)/chain of identity(COI)* would have a direct impact on patients. COC/COI checks were incorporated throughout the manufacturing process and before product administration to the patient. Testing of the system used to create, control and trace COC/COI was included into process validation.
- Generation or *replication-competent retrovirus* (RCR) is a theoretical safety issue. So far no RCR has been detected in any clinical trial using Yescarta.
- *Insertional mutagenesis* due to integration of vector can potentially induce secondary malignancies. Risk mitigation was addressed by using a limited copy number per cell.

After pre-license inspection at Kite Pharma and at a CMO responsible for retroviral vector manufacturing, FDA issued a Form 483 for each site. Both companies responded to the observations and the corrective actions were reviewed and deemed acceptable.

CAT/EMA Concerns on CMC

A major objection was related to the fact that consistency of transduction of the autologous cells had not been fully demonstrated. On the basis of responses and clarification provided by Kite Pharma, together with various commitments, the issue was considered resolved.

4.2.2 Environmental Risk Assessment (ERA)

Potential risks for the environment associated with the clinical use of YESCARTA are:

- Generation and transmission of RCRs
- Transmission of residual infectious retroviral vector particles
- Transmission of genetically modified T cells

FDA Concerns on ERA

A request for categorical exclusion from ERA has been accepted by FDA as manufacturing of Yescarta will not significantly alter the concentration and distribution of naturally occurring substances.

CMDH/EMA Concerns on ERA

Since either the likelihood of the identified risks or the potential hazards have been evaluated to be negligible, the overall environmental risk has also been concluded as negligible.

4.2.3 Non-Clinical Pharmacology and Toxicology

Kite Pharma submitted literature studies, *in vitro* and *in vivo* non-clinical non-GLP pharmacology data for Yescarta.

Primary Pharmacology

The following primary pharmacodynamic studies have been conducted:

- Comparability between products manufactured at two sites regarding transduction efficiency, similarity for in-process parameters, potency and cell growth profiles.
- CD19 expression profile summary based on literature search
- *In vitro* characterisation of human Anti-CD19 CAR-T cells in regards to specificity, potency, biological activity and composition.
- *In vivo* non-GLP studies using a murine model of lymphoma and anti-murine CD19 CAR-T cells as a surrogate for studies of the human anti-CD19 CAR-T cell product.

No secondary pharmacodynamic, safety pharmacology and pharmacodynamic drug interactions studies have been conducted.

Pharmacokinetics

Biodistribution was evaluated in the syngeneic mouse lymphoma model using flow cytometry analysis. No other non-clinical pharmacokinetic analyses were performed.

Toxicology

On-target/off-tumour toxicity of CD19 CAR-T cells has been included into the non-GLP primary pharmacology study using a murine model of lymphoma and anti-murine CD19 CAR-T cells.

No toxicity studies have been performed regarding single dose, repeat dose, reproduction, toxicokinetic data or local tolerance.

No *in-vitro* or *in-vivo* genotoxicity and carcinogenicity was assessed. The risk of retroviral vector insertional mutagenesis and potential carcinogenicity was addressed by performing a literature review for T cells transduced with retroviral vectors.

FDA and CAT/EU Concerns on Non-clinical Development

The non-clinical documentation submitted was considered adequate.

4.2.4 Clinical Development

In total, Kite Pharma has six Phase I/II, three Phase II, one Phase III and one expanded access study ongoing [61].

The clinical study ZUMA-1 (NCT02348216) provided the basis for the BLA and the MAA. ZUMA-1 is a single-arm, open-label, multicenter Phase I/II study for refractory aggressive B-cell non-Hodgkin lymphoma. Primary efficacy endpoint was overall remission rate (ORR), including complete remission (CR). In the Phase II part, 101 of 111 patients who underwent leukapheresis received Yescarta. The ORR was 72%, the CR rate 51% and partial remission rate 21%.

Safety issues of Yescarta are related to the mechanism of action. CRS occurred in 94%, neurologic toxicities in 85% and hypogammaglobulinemia occurred in 15% of patients following Yescarta. Four deaths were attributed to the product as per FDA analysis.

4.2.5 Post-Authorisation Obligations in the US

FDA determined that a REMS is indicated to ensure that the benefits of Yescarta outweigh the risks of CRS and neurologic toxicity.

In addition as post-marketing requirement (PMR), a multicentre, prospective, observational safety study will include 1500 subjects enrolled within 3 months of the Yescarta infusion over 5 years. All enrolled subjects will be followed for 15 years from their infusion. The primary endpoint will be evaluation for secondary malignancy.

4.2.6 Post-Authorisation Obligations in the EU

The CAT considers it necessary to address safety issues in a non-interventional post-authorisation safety study (PASS) based on a registry to assess the safety profile in patients with B-lymphocyte malignancies in the post marketing setting. Additional requirements of the marketing authorisation were: PSUR, agreed Risk Management Plan and an educational program which must be agreed with the National Competent Authority prior to the launch of Yescarta in each Member State.

4.3 Regulatory Activities and Tools Used for Kymriah and Yescarta

The regulatory history leading to the authorisation of Kymriah in the US and Europe is summarised in Table 3, for Yescarta in Table 4.

Table 3: Regulatory History and Tools Applied to Kymriah in the US and EU

		2013	2014	2015	2016	2017	2018
US	ALL	pre-IND Meeting (Apr)	pre-IND Meeting (03 Mar) SPA (Apr) IND Submission (Sep)	Orphan Designation (Mar)	Breakthrough Therapy Designation (Feb) Pre-BLA Meeting (Nov)	BLA Submission (Feb) Rare Paediatric Disease Designation (Mar) **BLA Approval** (Aug)	
US	DCBCL					Breakthrough Therapy Designation (Apr) Pre-sBLA meeting (Aug) Orphan Designation (Aug) sBLA Submission (Oct) sBLA Submission for changes in manufacturing (Nov)	**sBLA Approval** (May)
EU			EMA SA (Apr) Orphan Designation ALL (Apr)	PIP ALL	EMA SA (Apr) PRIME Designation (Jun) Orphan Designation DLBCL (Oct)	EMA SA (Jul) EMA SA (Sep) PIP DLBCL MAA Submission (Nov)	**MAA issued** (Aug)

Table 4: Regulatory History and Tools Applied to Yescarta in the US and EU

	2014	2015	2016	2017	2018
US	Orphan Designation DLBCL (Mar) IND Submission (Dec)	Breakthrough Therapy Designation (Dec)	Pre-BLA Meeting (Oct) BLA Submission, (rolling submission) First module (Dec)	BLA Submission, (rolling submission) Final modules (Mar) **BLA Approval** (18 Oct)	
EU	Orphan Designation DLBCL (Dec)	EMA SA (Jul & Dec)	PRIME Designation (May)	EMA SA (Feb & Sep) PIP MAA Submission (Jul)	**MAA issued** (Aug)

5 CAR-T Cell Development: Requirements & Challenges

The main objective of medicines regulation is to ensure safe and effective products are approved. CAR-T cell therapies are complex products that require a tailored approach, such as the risk-based approach (RBA) when planning the development of this class of products [67]. RBA, which is a unique feature to ATMPs, aims to determine the extent of quality, non-clinical and clinical data required to be included in the MAA of a specific product. An EMA guideline on RBA has come into effect in 2013 [24]. The methodology is based on the identification of risks and associated risk factors of an ATMP and the establishment of a specific profile for each risk. The identified risk profile should justify the extent of data included in the MAA dossier.

Examples of risks associated with CAR-T cell therapy are especially unwanted immunogenicity such as CRS, tumour formation, treatment failure, neurotoxicity and off tumour/on target toxicity and will be addressed later in chapter 5.3.3.

In the following chapters the main challenges during CAR-T cell development will be described and risk factors identified. Although CAR-T products may differ regarding their specificity, an overview of non-clinical and clinical studies required during development will be given and a potential regulatory strategy will be described.

5.1 Chemistry, Manufacturing and Control

Quality plays a major role in the safety and efficacy profile of CAR-T cell products. Due to the biological nature of their starting material and intricacy of the manufacturing process, critical quality attributes (CQA) of CAR-T cell products have a higher variability than chemical drugs. In addition, smaller study populations may result in the need for fewer manufacturing runs, which can make it difficult to establish the critical process parameters (CPP) necessary for ensuring CQA. However, a well-controlled manufacturing process along with suitable analytical assays to ensure a consistent product with predefined CQA for potency, identity and purity is of utmost important and should be established as early in development as possible, optimally before the first administration to humans [22,45]

The new EMA GMP guideline for ATMPs is built on a risk-based approach [22], to give the necessary flexibility for early clinical development and for production of

small volumes or batches. On the other hand, it also brings responsibilities for the manufacturers to set up control and mitigation measures suitable to the risk of the product and of the manufacturing process. When evaluating the risk to define the control and mitigation strategy, the characteristics of the product and the starting material, raw materials, level of manipulation and assessment of overall impact of the manufacturing process on the final quality, safety and efficacy of the product play an essential role.

However, the risk-based approach is assuming a staggered approach and gradual increase in the knowledge of the product and the process from the first stages of the development up to submission of an MAA to establish target product profile (TPP) and CQA. In parallel to this it is anticipated that manufacturing procedures and control methods become more detailed and specific during the more advanced phases of development.

The following challenges/risk factors related to CMC have to be particularly considered for a CAR-T cell therapy:

- *Manufacturing failure*
  A robust manufacturing process including controls should be in place prior to start FIH studies to prevent “drop outs “ due to manufacturing failures.
- *Process qualification and validation*
  Required patient derived material is a scarce source. The use of material from healthy donors can be used if properly justified, but blood composition differs significantly between healthy donors and cancer patients which can cause complications during development. Also ethical reasons might prevent the use of healthy donor cells.
- *Status of T cells*
  For autologous cell therapies it is crucial to obtain sufficient starting material from the patient that is suitable for activation and genetic modification. Depending on the seriousness of the cancer disease T cells may be in a status not satisfactory for CAR-T cell therapy. Appropriate selection criteria for enrolment of patients can help to prevent this issue.
- *Generation of replication-competent viral vector*
  During the manufacturing process replication-competent viral vectors could be generated and transferred to the patient. So far this has not occurred for CAR-T cell therapies. To avoid this issue, thorough purification of product to eliminate viral impurities is advisable.
- *Insertional mutagenesis*
  Malignancies can be induced by inadvertently activating cellular protooncogenes or disrupting tumour suppressor genes. This can be prevented by a specific vector design (e.g. “self-inactivating design”) or by

a limited copy number per cell. This issue is also addressed in chapter 5.2.

- *Cellular and viral impurities*
  The final product should not include other cell types than the transfected T cells and no free viral vector particles. Accurate T cell isolation and selection of transfected T cells is an important step during manufacturing and needs to be carefully controlled.

Complex distribution logistics are another characteristic of cell therapies. Cells are obtained from the patient via leukapheresis in a hospital setting and transported to the manufacturing site for genetic modification and final drug product generation. Final release testing occurs either at the manufacturing site or the product must be transferred to the relevant contract laboratory. After release the drug product is shipped back to the hospital for infusion into the patient. All these shipments need to occur refrigerated or frozen and the national requirements for shipment of GMOs need to be taken into account.

Due to the personalised approach and company specific manufacturing process it is not possible to design a more precise procedure for the CMC part.

5.2 Non-Clinical Development

The aim of non-clinical studies is to demonstrate the proof-of-concept and to define pharmacological and toxicological effects that may predict the efficacy and safety profile in humans. Compared to the extensive non-clinical programme of chemical medicinal products, no standard approach is available for CAR-T cell therapies yet and in general only a reduced set of studies is performed of which the majority of data is required prior to the first in human (FIH) study [17,20,51]. The extent of non-clinical data needed strongly depends on the risks related to the product, clinical experience with similar products and scientific knowledge and must be determined on an individual case-by-case basis.

The aim of non-clinical studies is to support dose selection for clinical trials, route of administration and application schedule. However, as CAR-T cells proliferate *in vivo*, non-clinical dose selection studies are not informative and dose selection for FIH studies is based on clinical experience with related products.

Non-clinical studies should be performed in relevant animal models showing a biological response to the product. To avoid xenoreactions and transgene product species-specificity, homologous animal models or immune-deficient animals might be used. Where appropriate *in vitro* and *in silico* analyses are also acceptable.

In general, pivotal non-clinical studies should be carried out according to GLP. However, due to the specific characteristics of the CAR-T cell therapy and its associated graft-versus-host reaction, it is not always possible to conduct such studies in commercially available animals under GLP and non-GLP studies are acceptable. For example, sometimes toxicology data are collected in POC studies that use an animal model of disease and are not available at a GLP testing facility. All in all, it is known for CAR T cell developments that *in silico*, *in vitro* and *ex vivo* nonclinical analyses fairly outweigh nonclinical studies performed in *in vivo* models due to the lack of appropriate models.
In case at nonclinical level a distinct safety or toxicity parameter cannot be evaluated and addressed sufficiently due to the limitation of the nonclinical modelling this parameter must be mitigated in the clinical situation with a risk-mitigation plan in place resulting in very close monitoring of the patient.

The minimum set of pharmacodynamic and pharmacokinetic studies comprises:

- Expression profile of corresponding tumour antigen based on literature search (CD19 for Kymriah and Yescarta)
- *In vitro* proof-of-concept (POC): characterisation of human CAR-T cells in regards to specificity, potency, biological activity and composition.
- *In vivo* POC: assessment of anti-tumour activity either in a xenograft tumour model (Kymriah) or in a mouse model with the murine surrogate CAR-T cells (Yescarta).
- *In vivo* biodistribution needs to be performed to address persistence, mobilisation and shedding of the product

The following aspects regarding toxicology must be assessed:

- Virus-specific toxicities
    - Generation of replication-competent virus during manufacturing
    - Unintended mutagenesis is evaluated via genomic insertion site analysis of the viral vector into the human genome either in vitro (Kymriah) or based on literature search (Yescarta).
- On-target/off-tumour and off-tumour toxicity needs to be addressed in an animal model or by combination of *in silico* and *in vitro* analyses.
- Immunotoxicity, if possible in a non-clinical setting.

In case significant changes in the manufacturing process or formulation may impact e.g. comparability of the later-phase investigational medicinal product (IMP) to the IMP used in early-phase clinical trials, an additional *in vitro* and/or *in vivo*

non-clinical bridging programme needs to be set up to compare both IMPs in its characteristics side-by-side.

5.3 Clinical Development

The purpose of clinical trials is to allow a benefit-risk assessment based on the characteristics of the product, the target indication and the existing treatments.
As for the quality and non-clinical part a risk based approach may also be chosen for clinical development to determine the extent of clinical data to be included in the MAA.
The therapeutic procedure for CAR-T cell products comprises the whole process starting with the collection procedure via leukapheresis, the lymphodepleting regimen, up to administration and potential concomitant medication such as immunosuppression [49]. Therefore, distinct features of CAR-T cell therapies need to be considered, such as

- Manufacturing peculiarities, e.g. collection and handling of source material
- Limited extrapolation from animal data on starting dose, biodistribution, immunogenicity and on- and off-target effects
- Uncertainty about side effects, immunogenicity and persistence in humans
- Uncertainty about tumorigenicity in case of integrating vectors
- Need for long-term efficacy and safety follow-up due to persistence of cells
- Concomitant medication, e.g. lymphodepleting chemotherapy

In exploratory, early-phase clinical trials the primary objective is the evaluation of safety, including an assessment of potential adverse reactions and an estimation of the relationship to dose. In the case of cellular immunotherapy feasibility of administration and pharmacological activity is also often assessed. The trials are therefore often designed as Phase I/II trials with DSMB (Data and Safety Monitoring Board) decisions, combining features of Phase I and Phase II design.

5.3.1 Study Population

Choice of subjects to include in a trial affects the ability to detect the product's beneficial activity or its potential side effects. The objective is to obtain an acceptable balance between the anticipated risks and potential benefits, while achieving the study's objectives.
Clinical trials with CAR-T cell therapy are conducted in patients and not in healthy volunteers. The disease stage plays an important role. Subjects with a more

advanced disease and a high medical need may be in a situation to accept higher risks and the risks might be more justified. They may also have the greatest need for benefit. However, the ability to detect evidence of any benefit could depend on the stage of disease and an anticipated effect might be more clearly distinguishable in subjects with a milder disease. In addition, subjects with severe disease might have confounding adverse events related to the stage of the disease.

Another point to consider is that manufacturing of CAR-T cell therapy may take weeks or months. A subject meeting the study enrolment criteria at the time of cell collection might no longer meet the criteria several weeks later at the time point planned for product administration or – in the worst case – already died. The condition of the subject may have deteriorated and may not survive for the study duration. To prevent this situation, enrolment criteria should include selection for factors improving the likelihood that a subject would still be suitable for product administration when the manufacturing process is complete.

5.3.2 Starting Dose, Treatment Plan & Follow-up

The starting dose should be chosen to show a pharmacological effect and must be safe. In case non-clinical data are not satisfying a search on similar products starting doses is useful. Factors determining the dose include the total number of cells administered, transduction efficiency, mean number of vector copy sequences integrated per cell and cell viability.

The first patient in a FIH trial should be intensively monitored for adverse events, taking into consideration also delayed onset of adverse events. Waiting periods between the first and the subsequent subject of a cohort followed by a safety assessment are essential (“staggered enrolment”). Tight monitoring of patients is crucial and along with a risk-mitigation approach should contribute to patients safety.

Classical dose-finding studies are not applicable, due to the *in vivo* proliferation and expansion of CAR-T cells. While higher CAR-T cell doses have shown higher toxicity, additional factors such as disease burden and antigen expression also contribute to toxicity [5].

To understand the pharmacokinetics of CAR-T cell therapy, CAR-T cell levels and their expansion and persistence in blood and target tissues at relevant time points

should be analysed, taking into account the effect of concomitant medicines, such as steroids.

A follow-up period of approximately 1 to 5 years is appropriate for an early-phase trial to provide preliminary evidence of efficacy and information on durability of activity. In addition, long-term follow-up is necessary to have an acceptable balance of risks and benefits, with the focus on long-term survival and serious adverse events [49].

5.3.3 SAFETY

CAR-T cell therapy is known to elicit acute toxicities that are linked to their pharmacologic and pharmacodynamic properties. Based on the experience with CD19 targeting CAR-T cells in leukaemia and lymphoma patients, the most critical adverse drug reactions (ADR) are cytokine release syndrome, neurotoxicity, tumour lysis syndrome (TLS) and on-target/off-tumour recognition causing e.g. B cell depletion [67,69]. In addition, adverse reactions may also be linked to the underlying malignancy, the apheresis procedure or the lymphodepleting chemotherapy.

In order to support a RBA the risks need to be precisely characterised, risk factors identified and risk mitigation strategies need to be in place.

CYTOKINE RELEASE SYNDROME

All patients treated with CAR-T cells experience some level of CRS, as it is part of the efficacy of the product. CRS is caused by high activation of T cells and destruction of numerous tumour cells at the same time (tumour lysis syndrome), both releasing large amounts of cytokines, especially IL-6. Signs and symptoms associated are high fever, fatigue, nausea, hypotension/tachycardia and cardiac dysfunction. Eventually, progression to multiorgan failure may occur.

Clinical experience has shown that high expansion rates of CAR-T cells are associated with severe CRS requiring careful consideration of the clinical dose and follow-up of the growth kinetics of CAR-T cells *in vivo*.

The currently preferred treatment is administration of tocilizumab, a therapeutic IL-6 receptor blocking antibody, which does not affect CAR-T cell persistence in the patient [68].

Neurotoxicity

Neurologic toxicities have been reported after CAR-T cell therapy [69], also known as CAR-T-cell related encephalopathy syndrome (CRES). Mild manifestations include confusion, aphasia or ataxia. The severe CRES encompasses seizures, cerebral oedema or encephalopathy. Several deaths were also reported due to neurotoxicity caused by cerebral oedemas and in some patients CAR-T cells have been found in cerebrospinal fluid. It is hypothesised that increased blood-brain barrier permeability resulting from systemic inflammation enhances transfer of lymphocytes and cytokines into the central nervous system.

To treat severe neurotoxicity systemic corticosteroid administration such as dexamethasone is the current practice [69].

Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) is the result of rapid tumour cell death leading to metabolic disturbances such as hyperuricemia and hyperkalaemia (elevated uric acid and potassium blood levels, respectively). Control of TLS can be obtained by either reducing the tumour size before CAR-T treatment or by lowering the amount of infused CAR-T cells or by combining both measures.

On-Target/Off-Tumour Toxicity

If the tumour associated antigen, for which the CAR is specific, is expressed on normal tissues, this tissue can be damaged by CAR-T cell therapy. This is the case for anti-CD19 CAR-T cell therapy, which also attacks B cells and can lead to diminished antibody production (hypogammaglobulinemia) and elevated risk of infections. In general, replacement therapy with immunoglobulin infusion can effectively manage this drawback.

5.3.4 Efficacy

Confirmatory trials should follow a randomised controlled design, comparing CAR-T cell therapy to a reference regimen, such as chemotherapy followed by autologous stem cell transplantation for high grade lymphoma.

Disease-free Survival (DFS), Event-free Survival (EFS), Progression-free Survival (PFS) and Overall Survival (OS) are generally accepted end points in confirmatory endpoints, while ORR and Duration of Response (DOR) are considered more appropriate in exploratory trials.

It is of interest to note, that both Kymriah and Yescarta obtained conditional marketing approval based on exploratory Phase I/II results of single-arm, open label studies with a number of 63 and 101 patients respectively receiving CAR-T therapy. However, for both products the approvals are conditional with the post-authorisation obligations including several Phase II PAES studies as well as a Phase III study to receive full approval.

5.4 Long-Term Follow-Up

CAR-T cell therapy is designed to provide life-long persistence of the biological activity. Due to this characteristic it is important to assess the product persistence by an appropriate follow-up period to generate long-term efficacy and safety data even after marketing authorisation. For the two licensed CAR-T cell products a follow-up period of 15 years is requested for the Phase III clinical trials. . This is also applicable for future GTMP developmental/approved drugs in the EU and the US.

5.5 Environmental Risk Assessment

An environmental risk assessment (ERA) is mandatory for a dossier of an MAA [70]. The ERA is based on the use of the product and the properties of the active substance and is aiming to protect the aquatic and terrestrial ecosystems [66].
In the case of CAR-T cell therapy the risks to the environment are mainly linked to the viral vector. It is very important to know and a specific requirement in the EU for GTMPs that also during clinical development an ERA as well as an GMO SNIFF document is the pre-requisite to get approval for a clinical trial application including FIM.

5.6 Regulatory Strategy for a CAR-T Cell Therapy

Due to the complex nature of CAR-T cell therapies and the lack of an “off-the-shelf” development strategy, it is strongly recommended to contact the relevant regulatory authorities early during development and maintain an ongoing communication. The examples of Kymriah and Yescarta have shown, that the use of specific regulatory tools can help to speed up the development time.
Depending on the country an applicant wants to submit the application, two scenarios are described, one for the EU and one for the US, based on the assumption that the CAR-T cell therapy is developed to treat a rare disease, as is the case for most CAR-T therapies under development.

5.6.1 EXEMPLARY PATH TO LICENSE IN THE EU

To obtain marketing authorisation in the EU, the following procedure can be followed, also shown in Figure 4:

A dialogue with EMA can be initiated early in development with an Innovative Task Force meeting to prepare for EMA procedures. Orphan designation should also be requested early in development, as many valuable incentives are provided with this designation, such as fee reductions. ATMP classification of the CAR-T therapy can occur prior to non-clinical development. This can be obtained by EMA or by a national authority. If a CAT certification is wanted for e.g. out-licensing activities or peer review of data, quality and non-clinical data should have been generated for the scientific evaluation and compliance check with Annex I to directive 2001/83/EC.

Prior to initiate an FIH clinical trial, a scientific advice or protocol assistance meeting with CAT in cooperation with the Scientific Advice Working Party (SAWP) should be requested to discuss if the available CMC and non-clinical data package is sufficient to support the planned FIH clinical trial. In addition, the study synopsis is presented and discussed. Based on the outcome of the SA/protocol assistance meeting, the clinical trial application (CTA) for the FIH clinical trial can be prepared and submitted in the EU at each country-specific national level. Upon preliminary clinical evidence PRIME designation can be requested and with this the rapporteur for the centralised procedure will be appointed. Based on early clinical data on efficacy, another SA at EMA should be requested to obtain the agency's opinion if the FIH can be the basis of the MAA and to discuss the possibilities of an adaptive pathway procedure leading to a conditional marketing authorisation. The option of accelerated assessment should also be evaluated during this meeting. If consensus is reached within CAT/SAWP, the MAA can be prepared and submitted. If a conditional marketing authorisation is granted, several post authorisation obligations will be requested, such as observational and interventional PAES Phase II and III studies. Protocol Assistance can also be requested for these studies.

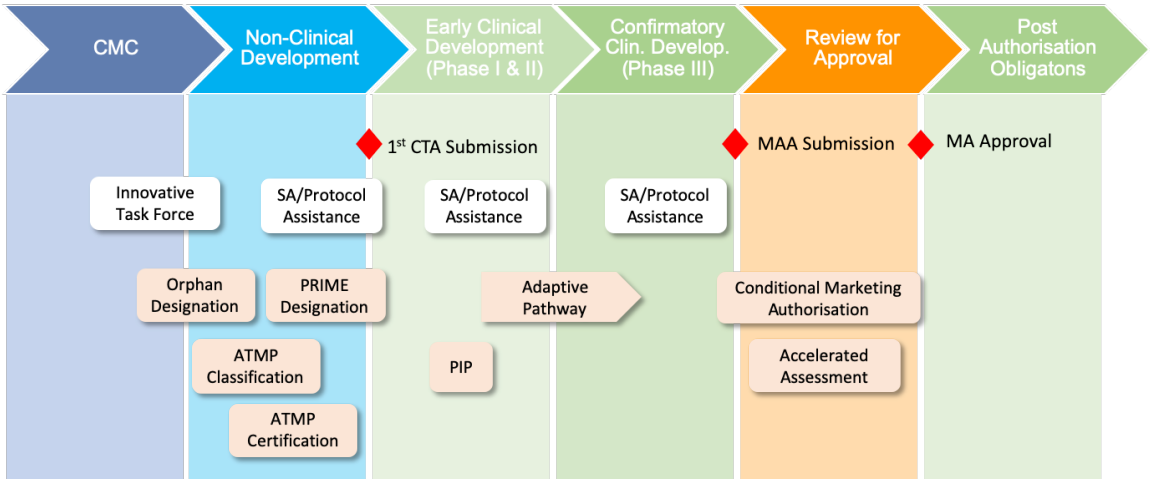

Figure 4: Regulatory strategy for CAR-T cell therapy in the EU. CTA: Clinical Trial Application, MAA: Marketing Authorisation Application, MA: Marketing Authorisation, SA: Scientific Advice, ATMP: Advanced Therapy Medicinal Product, PIP: Paediatric Investigational Plan.

5.6.2 Path to License in the US

For licensure in the US, the following procedure is suggested and visualised in Figure 5:

The first type of meeting with the FDA can be an INTERACT meeting to obtain initial, non-binding advice from FDA on CMC and testing strategies and on pharmacology and toxicology topics, e.g. the suitability of a selected animal model or the acceptability of *in vitro* and *in silico* preclinical testing strategies. Initial general recommendations on a future FIH trial in a target clinical population can also be discussed.

When manufacturing has further matured, the non-clinical data set planned and mostly finalised and the protocol synopsis for the FIH clinical trial has been developed, a pre-IND meeting should be requested at FDA. Based on the CMC and non-clinical plans and data package submitted to FDA, the authority gives feedback on whether the CMC and non-clinical plans are adequate and appropriate to move into the proposed FIH clinical trial. Assuming that the FIH clinical trial might also be the basis for the BLA, as seen for Kymriah and Yescarta, a Special Protocol Assessment can be requested to obtain FDA commitment to accept the study results for filing.

The orphan designation should be requested as early as possible during development and Fast Track designation as soon as convincing non-clinical data are available.

Based on FDA's feedback during the pre-IND meeting and after SPA, the IND package can be prepared and submitted.

Once preliminary efficacy data of the FIH clinical trial are available, RMAT designation can also be requested. In addition, an End-of-Phase I (EoPI) meeting with FDA should be planned to discuss if the ongoing clinical trial might be sufficient as basis for a BLA and if Accelerated Approval should be considered. If FDA agrees, a pre-BLA meeting can be scheduled to discuss filing and format issues and to prevent any refuse-to-file issues. Priority Review designation and Rolling Review should also be discussed during the pre-BLA meeting. After BLA submission, FDA reviews the application and issues or rejects approval. A BLA approval based on a phase I/II trial will require several post authorisation obligations, such as additional interventional and observational studies as well as a REMS.

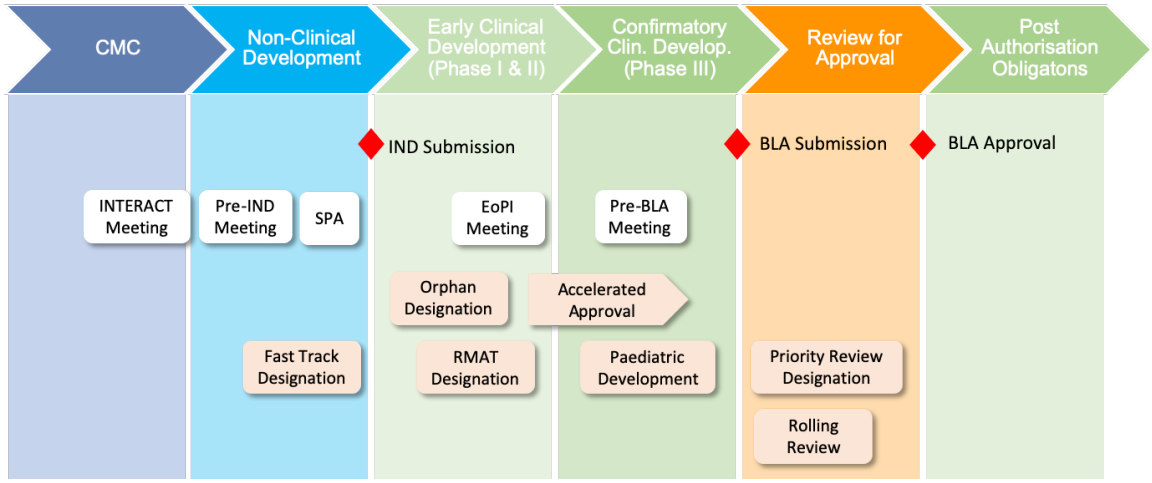

Figure 5: Regulatory strategy for CAR-T cell therapy in the US. IND: Investigational New Drug, EoP: End of Phase, BLA: Biologics License Application, SPA: Special Protocol Assessment.

If the intention is to obtain a marketing authorisation for both regions, the EU and the US, it is useful to align the scientific advice meetings prior to the FIH phase. The meetings with both authorities should occur within the same timeframe so that suggestions from both authorities can be implemented in the study protocol and

considered for endpoint definition. Alternatively, a parallel scientific advice with EMA and FDA can also be requested.

6 Discussion and Conclusion

In the previous chapters the regulatory requirements and available regulatory tools for CAR-T cells have been described for the EU and US. Both regulatory landscapes include mechanisms for early dialogue with the agencies as well as tools to expedite drug development. Although there is no difference in numbers of approved CAR-T cell therapies when comparing the US and the EU market so far (Kymriah and Yescarta, see chapter 4), the number of ongoing CAR-T cell clinical trials within the US by far exceeds the one in Europe: 312 CAR-T cell therapy trials are ongoing in the US compared to 118 in the EU [61].

A direct comparison between the situation in the US and the EU is challenging. The most prominent difference between the two regulatory ICH regions is the political structure. Whilst the US is a single country with the FDA being the only national authority providing harmonised provisions throughout, the EU is a union of multiple countries with distinct national specialities. Despite all harmonisation efforts, differences still exist especially in CAR-T relevant issues, such as requirements for clinical trial approval. For example, CAR-T cells are classified as genetically modified organisms (GMOs) in certain EU member states, requiring an environmental risk assessment as well as a release certificate prior to clinical evaluation. Variable approval timelines for multi-centre trials in several EU member states can also complicate the initiation of a trial. The new EU Clinical Trial Regulation 536/2014 should help to harmonise the situation once in place.

In general, a company developing a CAR-T therapy intends to market the product in both regions, the EU and the US. It should aim for a “harmonised” development plan, meaning that the clinical trial which is supposed to serve as the basis for conditional approval, satisfies the requirements of both authorities. As described in chapter 5.6 this can be obtained either via separate scientific advice with both authorities within the same period of time or via a parallel scientific advice with EMA and FDA.

Car-T cell therapy requires an infrastructure providing capacities for viral vector generation and GMP manufacturing of CAR-T cells of high quality and consistency associated to a hospital. The clinical trial should take place where the required

infrastructure is available, as this is the most critical element of CAR-T therapy. Compared to the US, there are only a few places in the EU that can provide this [5].

If there is a choice either because development is at a very early stage and no infrastructure has been set up yet, or because clinical collaborations exist in both regions, it is advisable to run the clinical trial in the US rather than in the EU.

Another advantage of choosing the US for CAR-T development is the favourable environment for orphan drug development based on the Orphan Drug Act of 1983 [71]. As well as the extended market exclusivity of 7 years instead of 5 years, the Orphan Drug Tax Credit allows orphan drug developers to collect tax credits for expenses incurred for US clinical trials on the orphan designation. The Orphan Product Grant programme provides funding for clinical testing and in addition the orphan drugs are exempt from the usual new drug application or "user" fees charged by FDA [72].

Although EMA offers its own incentives for orphan drug development, they are less attractive than those offered by FDA. They include e.g. fee reduction for protocol assistance (75%) and marketing authorisation (10%), but no tax savings or funding for clinical trials.

A peculiarity of the European legislation is the "hospital exemption" (HE). Following the implementation of the ATMP regulation in 2008 [9], the centralised procedure became mandatory for ATMPs. As ATMP developers are mainly represented by SMEs and academic institutions with only limited regulatory expertise, personnel and budget, the requirements of the ATMP regulation represented an enormous burden. To prevent the regulation from acting as an innovation blocker, the HE was introduced into the ATMP Regulation to allow the use of certain ATMPs in individual EU member states without the need for a marketing authorisation. HE can only be applied for custom-made ATMPs used in a hospital setting for a specific patient. Such products are produced under the responsibility of a physician and are only to be used within the member state they are produced. HE enables patients to receive an ATMP under controlled conditions in cases where no authorised medicinal product is available. However, different interpretations across the EU have created a situation where HE might be used to circumvent the process of marketing authorisation via the centralised procedure. As an ATMP used within the HE framework can only be used in one Member State, there is the potential to

limit access to patients across the EU. In addition, especially for orphan medicinal products, recruitment for clinical trials can pose a substantial hurdle. Therefore, enrollment in a clinical trial should always be favoured in comparison to an HE product, as collection of evidence-based data should not be delayed in the interest of the healthcare community. Lack of transparency and information sharing are other drawbacks of HE, as there is no EU wide requirement for physicians using such products to collect data to establish whether the products are safe and effective (beyond the required pharmacovigilance reporting). So, although HE does not exist in the US regulatory framework, it does not represent a criterion to favour a development in the EU rather than in the US.

In final summary, development of CAR-T products follows a risk-based approach in both regulatory landscapes. It is a characteristic of this type of therapy, that the medicinal product not only distributes extensively in the patient's body but may also persist for a lifetime. Hence possible side effects may also occur for an extended period. Toxicology studies in animals contribute little to the overall knowledge base, but the risk of side effects is exceptionally high as previous clinical trials with CAR T cell products have shown, causing CRS, neurotoxicity, tumour lysis syndrome and on-target/off-tumour toxicity (see chapter 5.3.3). Moreover, although not observed in clinical trials with CAR-T products so far, insertional mutagenesis may be caused by viral vectors integrating into the host DNA. Pharmacovigilance and especially long-term follow-up are therefore of utmost importance for this kind of product. In the EU a "Risk Management Plan" is part of the MAA and is often modified during the review process based on agency feedback. As seen for Kymriah and Yescarta in Europe, a marketing authorisation has been granted based on additional requests to the RMP. In the US, the "Risk Evaluation and Mitigation Strategy" is not automatically part of the BLA submission but is requested for products with an elevated risk, such as CAR-T cell therapies. Both authorities, EMA and FDA, requested very long follow-up periods for both authorised products (Kymriah & Yescarta): the EMA 20 years, the FDA 15 years. These are relatively extensive periods and are a consequence of the lack of knowledge regarding long-term safety. From an authority perspective this is understandable. However, because CAR-T cells belong to the GTMPs, data archiving of 30 years after end of study is required in Germany. So, in total 45

years of data management are requested: a time frame that can be considered relatively long for SMEs which oftentimes have uncertain financial futures.

7 OUTLOOK

Intensive developments are ongoing worldwide to address issues related to manufacturing, cost of goods (COG), safety and efficacy, to name a few.

Universal CAR-T cells

A switch from autologous to allogeneic donor T cells could provide significant advantages if the MHC barriers were to be eliminated. Quality and quantity of T cells would improve if using a heathy T cell donor and if the time prior to administration could be reduced for patients with a severe disease status. In addition, manufacturing would be simplified, faster and less expensive, maybe even allowing “off-the-shelf” products but at least reducing the logistical complexity and COG [73].

Suicide Safety Switches

To mitigate the potential risk with CAR-T cell therapy, molecular systems to achieve inducible death of the genetically modified T cells have been developed. These so called “suicide switches” are incorporated into the CAR construct and can be activated by administration of a specific small molecule. Once the suicide switch has been turned on, the T cells undergo rapid apoptotic cell death. Severe adverse reactions could thereby be controlled by specifically depleting CAR-T cells in a controlled manner [74].

3rd Generation CAR and TRUCKs

Kymriah and Yescarta are 2nd generation CARs, which, in contrast to 1st generation CARs, contain a co-stimulatory domain to improve e.g. proliferation and cytokine secretion. 3rd generation CARs contain multiple co-stimulatory domains to improve effector functions and *in vivo* persistence compared to 2nd generation CARs. TRUCKs (T cells Redirected for Universal Cytokine-mediated Killing) are 4th generation CARs. They combine the expression of 2nd generation CARs with factors that enhance anti-tumoral activity, such as cytokines, co-stimulatory ligands or enzymes that degrade the extracellular matrix of solid tumours. The benefits and risks of the 3rd and 4th generation CAR-T cells remain to be explored in clinical trials [73].

Solid Tumours

CAR-T cell therapy has shown very good results in B cell associated malignancies, residing in tissues that are reached relatively easy. Solid tumours pose a higher challenge to CAR-T therapy. So far, attempts to target tumour-associated antigens in solid tumours have achieved only limited success due to the inability to reach and survive in the microenvironment surrounding the tumour [71]. A potential approach could be using CAR-T cell therapy recognising several tumour antigens, with the CAR being expressed either on one CAR-T cell (Multi-CAR T cell) or using a pool of CAR-T cell products [5].

Commercialisation of CAR-T cells

Due to the personalised approach, CAR-T cell therapies are associated with high costs. The list price of Novartis' Kymriah is $475,000 per single dose in the US. The UK's National Institute for Health and Care Excellence (NICE) made an agreement with Novartis at a price of £282,000 ($361,000) and for Germany Novartis has set a list price of €320,000 ($371,000), which will be subject to the usual negotiations and cost-benefit assessments with insurers [77]. "Pay for performance" or "outcome-based" contracts are also under discussion with health insurance companies. An example for this is the recent negotiations between Novartis and GWQ Service Plus, a representative of several health insurance companies in Germany. The agreement is based on the performance of the product: in case the therapy does not show the promised effect on a specific patient, Novartis will partially refund the price of its Kymriah medicinal product . The agreement should facilitate the use of CAR T anticancer therapy prior to finalization of the reimbursement negotiation with the "GKV Spitzenverband". However, details are not given so far, for instance how high the refund will be in case of non-performance of the therapy.

When compared to the financial burdens of effective but non-curative therapies to treat hematologic malignancies, a lifetime cost of $604,000 per patient is estimated (e.g. for Chronic lymphocytic leukaemia (CLL)). Having these numbers in mind, it is likely that CAR-T cell therapies are more cost-effective than current standard-of-care therapies for leukaemia and lymphoma [74,75]. Nevertheless, the current high costs will be a limiting factor for many countries whose health care systems will not be able to finance CAR-T therapy.

Regulatory

Clear regulatory guidance is important for the development of a new medicinal product. However, for innovative technologies such as the CAR-T cell therapy, relevant guidelines are often not established at the beginning of the process. Until harmonized regulations are available in the EU and there is common experience among different member states, a certain level of uncertainty in product development and a greater dependence on case-by-case regulatory assessment must be accepted. Yet several EU ATMP guidelines have been finalized in 2018 and some are under consultation until summer 2019 (see Table 1). Also, in the US several cellular & gene therapy guidelines were developed and published in 2018 and 2019 [see Table 2].

The long term effect of CAR-T cells as cancer therapy will be discerned within the next years following “provisional” approval of the CAR-T therapies, when post-approval clinical trials will help to define morbidity, mortality and efficacy of CAR-T cells [78].

CAR-T cell therapy represents a significant turning point in the field of cancer treatment. While their complexity challenges our perception of what a drug is and their production can be challenging, the success of these novel therapies inspires the continued expansion of drug development boundaries.

8 SUMMARY

CAR-T cell therapy represents a significant turning point in the field of cancer treatment and has given a lot of hope to cancer patients. The therapy is based on stimulating the patient's immune system and is designed to cure the disease with a single treatment.

While their complexity challenges our perception of what a drug is and their production can be challenging, the success of these novel therapies inspires the continued expansion of drug development boundaries.

In 2018, the first two products, Kymriah® (Novartis) and Yescarta® (Kite Pharma/Gilead), obtained regulatory approval in the EU for treatment of acute lymphoblastic leukaemia and diffuse large B-cell lymphoma, refractory to a standard chemotherapy regimen or relapsed after stem cell therapy.

In this master thesis the European and US regulatory environment and requirements for CAR-T cell therapy against cancer are summarised and the path to licensure of the two approved CAR-T cell therapies Kymriah and Yescarta analysed. Based on this, requirements and challenges for CAR-T therapy development are evaluated and a potential regulatory strategy for the EU and the US proposed. A final assessment on which ICH region to choose for CAR-T therapy development – the EU or the US – concludes the thesis.

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

Dr. Ornella Fumagalli