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# THE PROCESS OF CAR T CELL THERAPY IN EUROPE

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# THE PROCESS OF CAR T CELL THERAPY IN EUROPE

## EHA Guidance Document

These are exciting times for hematology and hematologists worldwide as innovations and advances in this medical field are rapidly emerging. Among the numerous new techniques and therapies being developed, immunotherapy stands out, providing promising new cancer treatment options such as chimeric antigen receptor-T cell therapy (CAR T cell therapy).

Current CAR T cell therapy involves the removal of a patient's own T lymphocytes and ex vivo genetic manipulation of these cells to create recombinant receptors with antigen-binding and T cell-activating functions. Once engineered (usually with the aid of a viral vector), CAR T cells are reintroduced to the patient, where they act as a "living drug," undergoing antigen engagement and amplification in the peripheral blood. From here, they travel to tumor sites, identifying and killing tumor cells expressing the corresponding antigen. Two commercial CAR T cell therapies are currently approved by the European Medicines Agency and the US Food and Drug Administration.

To ensure that all stakeholders involved in the use of new therapies receive appropriate education, the European Hematology Association (EHA) launched a new EHA program intended to raise awareness, provide education, stimulate further research, and build a network of experts in areas of high-impact hematology. One of the first of these "Topics-in-Focus" programs is tackling the high-impact issue of CAR T cell therapy. This document has been created to provide practical guidance for all stakeholders interested in introducing CAR T cell therapy, with a focus on European professionals. Those who might have a particular interest in CAR T cell therapy are listed in Box 1, although any group involved in this therapy should find the information provided useful.

To guarantee the reliability and safety of CAR T cell therapy, this document aims to define the optimal conditions to administer CAR T cell therapy, makes recommendations for health care professionals from each European Member State regarding the required organizational structure and accreditation for the use of this therapy, and stresses the need for a multidisciplinary approach in the implementation of CAR T cell therapy.



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## Guidance from the European Hematology Association

This document has been created to provide practical guidance for centers and national authorities in Europe that are interested in introducing chimeric antigen receptor (CAR)-T cell therapy. It will include European recommendations, based on both the latest scientific insights and on European Medicines Agency (EMA) guidance, to help the following groups optimize CAR T cell therapy in clinical practice. It is intended that:

- hematologists and other personnel at hematology centers are informed regarding the necessary requirements that need to be considered for CAR-T cell therapy,
- expert communities at the national level will be assisted when supporting national authorities during the establishment of criteria for center qualification,
- regulators at the European and national levels are informed regarding the hematology community's priorities for center qualification, and
- patients understand the need to be referred to CAR T cell accredited centers.

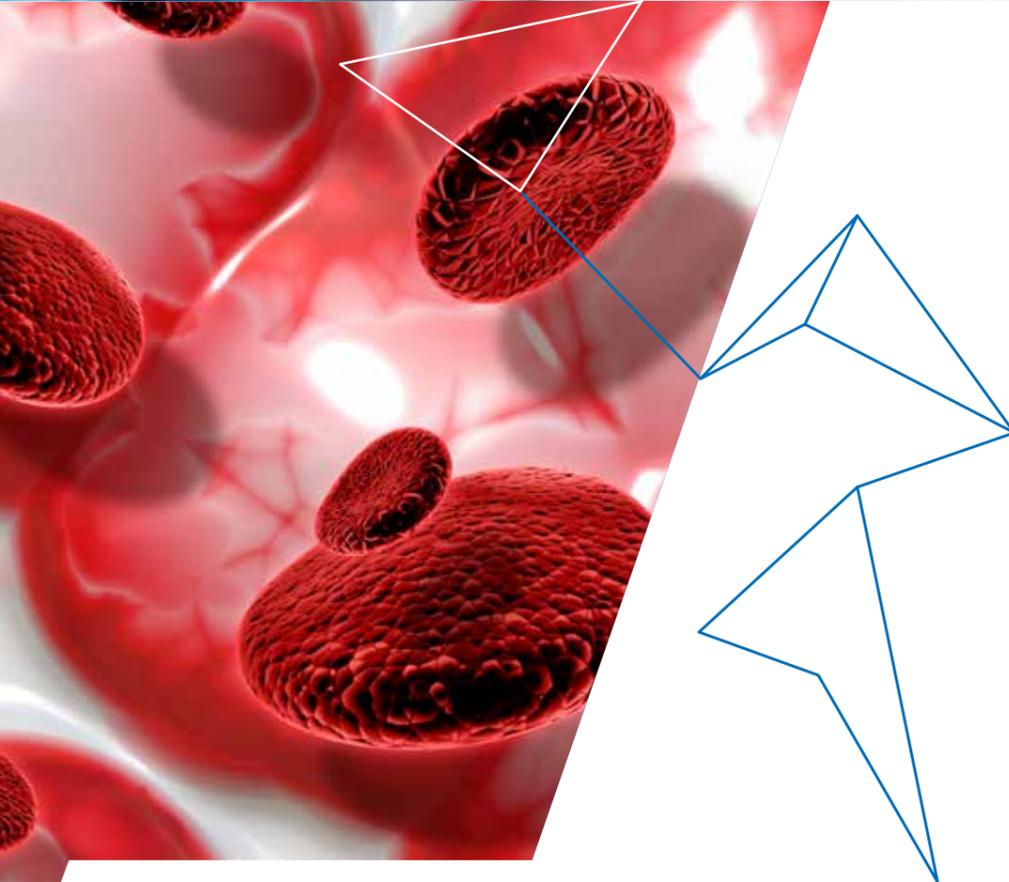
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# CAR T CELL THERAPY



Chimeric antigen receptor (CAR)-T cell therapy, or CAR T cell therapy, is a new class of adoptive cellular immunotherapy for cancer treatment. This cell therapy takes advantage of the natural ability of T cells to penetrate tissues, become activated and amplify, and eliminate target cells<sup>1</sup>.

CAR T cells are included in the regulatory category of advanced therapy medicinal products (ATMPs). The structure of consecutive generations of CARs (Figure 1), as well as the different steps in the CAR T cell therapy process, and the results and complications associated with commercial and academic CAR T cell therapy were recently reviewed in *HemaSphere*<sup>1-3</sup>.

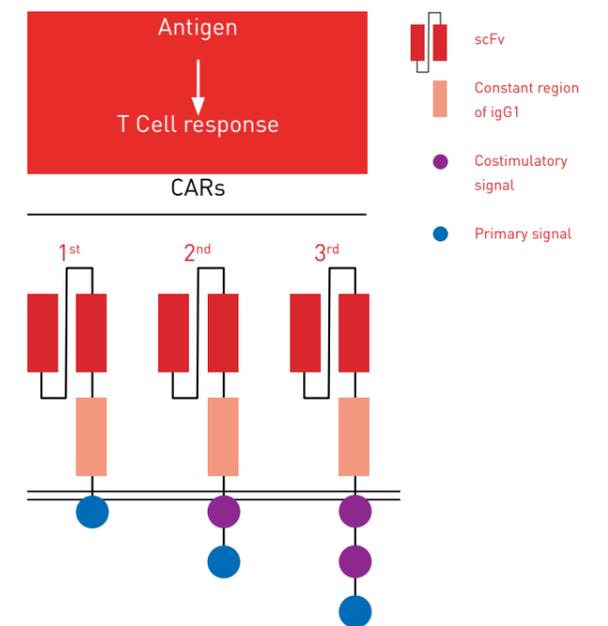


Figure 1. Structure of first-, second- and third-generation chimeric antigen receptors (CARs) (modified from reference 1). IgG1, immunoglobulin G1; ScFv, single-chain variable fragment

## 1.1 What is CAR T cell therapy?

In brief, CAR T cell therapy involves the *ex vivo* genetic manipulation of a patient's own T lymphocytes, using either lentiviral or retroviral vectors or non-viral gene transfer systems, to express engineered CARs specific for particular tumor targets (Figure 1)<sup>4-6</sup>.

These reprogrammed CAR T cells are then expanded, selected if necessary, and infused into the patient after they have received an immunosuppressive preparative regimen (Figure 2)<sup>2</sup>.

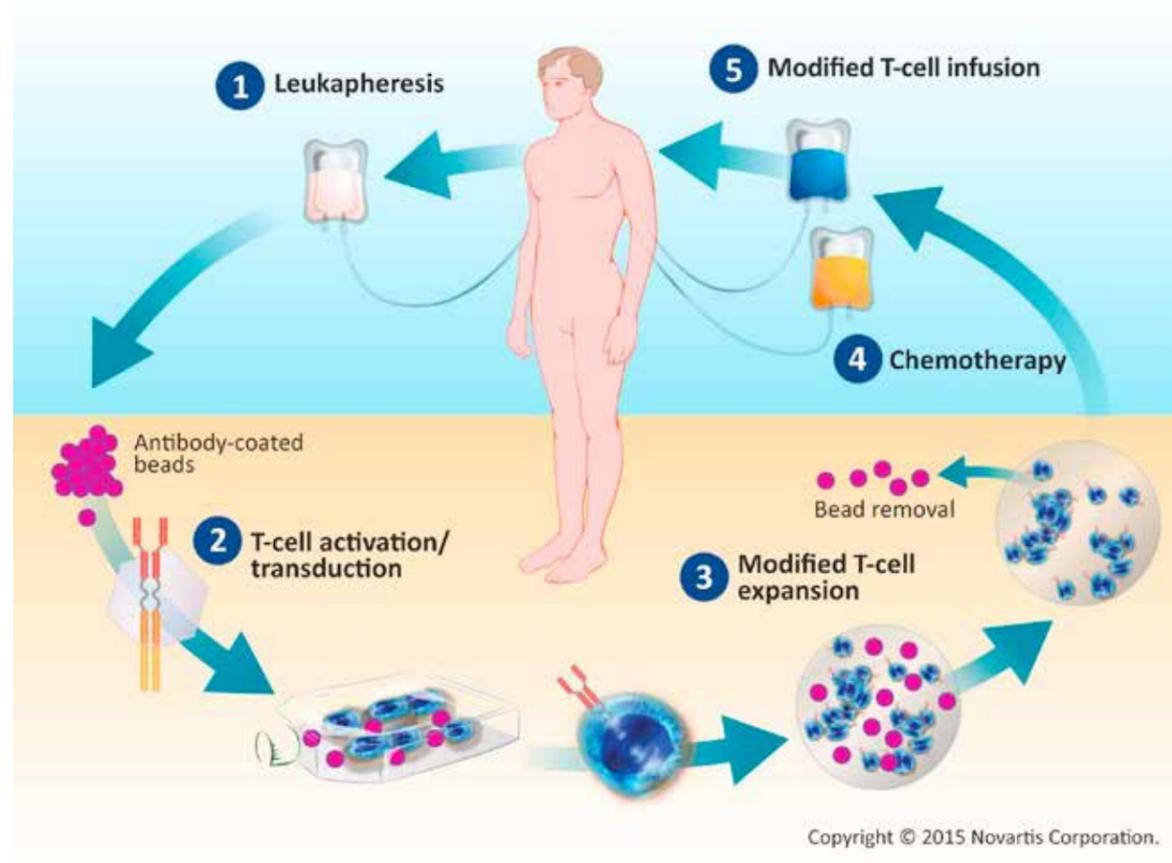


Figure 2. CAR T cell therapy process (from reference 2)

CAR T cells undergo antigen engagement and amplify in the peripheral blood, from where they travel to tumor sites and identify and kill tumor cells expressing the corresponding antigen. This can trigger extensive proliferation of CAR T cells and the release of tumor antigens, which activate the patient's immune system to recruit non-CAR T immune cells, thus eliciting further antitumor responses in a process known as cross-priming from epitope spreading<sup>7</sup>.

CAR T cells can persist in the body for years and can maintain long-term disease control if they persist in substantial numbers and have active effector functions<sup>8</sup>. For example, CAR T cells targeting the B-lymphocyte antigen CD19 may persist long term, leading to sustained control of the tumor and

prolonged B-cell aplasia of normal lymphocytes. However, disease relapse is frequently observed when the number of CAR T cells drops to undetectable levels. In most cases of CD19 CAR T cell loss, relapse was heralded by recovering healthy B cells; therefore monitoring of healthy B cell counts may help to identify patients with a high risk of relapse<sup>6,8</sup>. On the other hand, relapse may also occur because of the emergence of neoplastic B-cells that have lost CD19 expression<sup>6</sup>.

T cells redirected by second-generation CARs, as well as third-generation CARs under investigation<sup>9</sup>, show durable cytokine release, amplification, and anti-tumor activity, making them more suitable for clinical applications<sup>10-12</sup>.

## 1.2 Clinical trials of CAR T cell therapy

Currently, more than 492 clinical trials are listed as investigating CAR T cell therapy in the treatment of hematologic or solid cancers around the world, the vast majority of which are being performed in the USA and China (about 87%); a minority of trials are being performed in Europe<sup>13</sup>. More than 1000 patients have received anti-CD19 CAR T cell therapy in the USA alone<sup>1</sup>.

Preliminary data regarding CAR T cell therapy in Europe were presented at the First European CAR T cell meeting organized by the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) in February 2019.

At that meeting, it was first reported that at least 340 patients have been treated with CAR T cell therapy in Europe, most commonly (95%) in clinical trials<sup>14</sup>. In addition to the approved B-cell acute lymphoblastic leukemia (ALL) and B-cell lymphoma indications, CAR T cell therapy use is being extended to other hematological diseases such as chronic lymphocytic leukemia, multiple myeloma, Hodgkin lymphoma and acute myeloid leukemia as well as solid tumors. These latter indications are still under investigation in clinical trials, of note, encouraging responses have just been reported in patients with multiple myeloma<sup>15</sup>.

## 1.3 Need for CAR T cell therapy

Anti-CD19 CAR T cell therapies cover a significant unmet clinical need in B-cell ALL (B-ALL) and diffuse large B-cell lymphoma (DLBCL):

- Even though pediatric patients with newly diagnosed B-ALL achieve high complete remission (CR) rates and 5-year survival rates of over 90% when treated with combination chemotherapy<sup>16-18</sup>, 15–20% of children and adolescents with relapsed/refractory disease have considerably lower cure rates, and their prognosis has not significantly improved over the past two decades<sup>17,19-21</sup>
- Cure rates are low for adult patients with B-ALL<sup>22</sup>.

The recently introduced novel therapies, such as monoclonal or bispecific antibodies, or antibodies combined with immunotoxins, have improved CR rates and duration in patients with refractory/relapsed ALL; however, these novel approaches are not curative, and long-term survival remains poor<sup>23-26</sup>. Likewise, for DLBCL, published data indicate that patients refractory to chemotherapy or those who experience a second or subsequent relapse, particularly before 12 months after an autologous hematopoietic transplantation, have poor outcomes, with long-term survival not exceeding 20%<sup>27</sup>. New antibody-based therapies have shown promise but so far have not significantly changed the prognosis of DLBCL<sup>28</sup>.

## 1.4 Approved CAR T cell therapies

Tisagenlecleucel (CTL019, Kymriah™) and axicabtagene ciloleucel (KTE-C19, Yescarta™), both harboring second-generation CARs directed against CD19, were the first two CAR T cell therapies to be approved in the United States of America (US Food and Drug Administration [FDA]) and Europe (European Medicines Agency [EMA]). These therapies were also the first medicines supported through the EMA's PRiority MEDicines (PRIME) scheme to receive positive opinions from the Committee for Medicinal Products for Human Use (CHMP). The voluntary scheme provides early and enhanced scientific and regulatory support to medicines that have the potential to address, to a significant extent, patients' unmet medical needs. The different structure of these two CARs directed against CD19 has been reviewed elsewhere<sup>1</sup>.

In Europe,

- tisagenlecleucel** (Kymriah™) is approved for the treatment of patients up to 25 years of age with B-ALL that is refractory, in relapse post-transplant, or in second or later relapse and for adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy.
- axicabtagene ciloleucel** (Yescarta™) is approved for adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

Approved CAR T cell therapies and most CAR T cell therapies in development, including lisocabtagene maraleucel<sup>29</sup>, target CD19-positive cells and currently utilize autologous T cells, although the use of universal off-the-shelf allogeneic CAR T cells and natural killer (NK) CAR cells is also actively being investigated.

The technology and strategy of CAR T cell therapy that utilizes autologous, genetically modified, and adoptively transferred T cells for individualized cancer treatment is fundamentally different from that of available small-molecule or biologic therapies and—as with all new therapeutic modalities—introduces

new regulatory and logistic considerations for medical practice. CAR T cell therapy requires a complex care process that has similarities, in a hematology oncology context, to the logistics and/or complications of hematopoietic stem cell transplantation (HSCT) and high-risk novel anti-checkpoint immunotherapies<sup>3,30,31</sup>.

## 1.5 Potential complications of CAR T cell therapy

CAR T cell therapy is associated with a number of potentially severe complications (Figure 3), and its major toxicities have been summarized in recent reviews<sup>3,32</sup>. In some cases, complications may be potentially lethal. For this reason, expertise in, and a multidisciplinary approach to the use of this therapy is mandatory.

Although the frequency and severity of adverse events tends to vary across indications, the types of events reported are generally consistent. The most relevant is cytokine release syndrome (CRS), which, in its severe form, is reported in 27–38% of patients and correlates with high disease burden and greater CAR T cell expansion<sup>6,33,34</sup>. Another important complication is CAR T cell-related encephalopathy syndrome. This can be mild and self-limiting, resolving within days, but can manifest with confusion, delirium, hallucinations, aphasia, seizures, motor weakness, incontinence, reduced alertness, and cerebral edema<sup>33,35-38</sup>. In June 2018, the American Society of Blood and Marrow Transplantation convened a consensus conference to develop a common grading system for both CRS and neurotoxicity<sup>39</sup>.

In some patients, CRS appears associated coagulopathy, which requires frequent monitoring of fibrinogen levels<sup>39</sup>; in this situation, repletion with cryoprecipitate or fibrinogen concentrate is

mandatory to avoid bleeding complications, in addition to the anti-cytokine treatment. It is expected that the management of CRS will improve in the future as a consequence of current research to identify predictive biomarkers and of the early use of tocilizumab<sup>40-42</sup>.

Since CD19-directed CAR T cell therapy cannot differentiate between malignant and nonmalignant cells, depletion of normal B cells and hypogammaglobulinemia can occur, often continuing as long as CAR T cells persist in the patient<sup>33,36,37</sup>. Intravenous or subcutaneous immunoglobulin can be used, if necessary, to manage hypogammaglobulinemia on a regular basis in children (frequently every 4 weeks) and in adults (mainly those with recurrent infections)<sup>36,37</sup>.

Other toxicities reported in pediatric and young adult patients with B-ALL include neutropenia with high fever (61%), infections (44%), cytopenias not resolved after 28 days (35%), and tumor lysis syndrome (3%)<sup>33</sup>. In a phase II clinical trial in pediatric and young adult patients with B-ALL, tisagenlecleucel therapy was associated, in the first 8 weeks after infusion, with grade 3–4 CRS (46%), neurologic events (40%), infections (43%), cytopenias not resolved after 28 days (37%), febrile neutropenia (35%), and tumor lysis syndrome (4%)<sup>33</sup>.

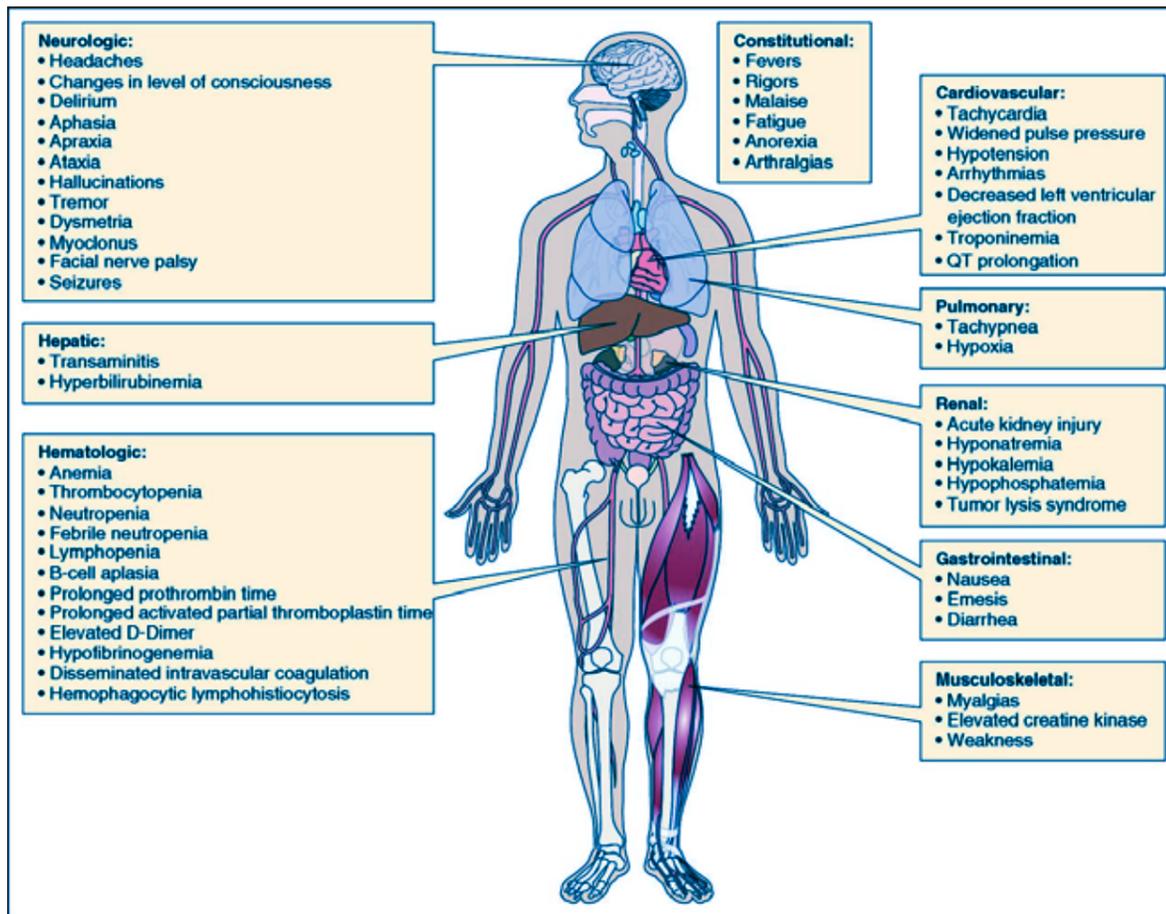


Figure 3. Described toxicity of anti-CD19 CAR T cell therapy (from reference 31)

## BOX 1: Stakeholders involved in the definition of the CAR T cell process

- ⊙ European and national authorities for drug authorization (specifically, ATMPs)
- ⊙ Ministries of Health of the Member States
- ⊙ European (EHA) and national societies of hematology, oncology, pediatrics, immunology, and pharmacy
- ⊙ European (EBMT) and national societies of hematopoietic transplantation and cell therapy
- ⊙ National representatives from clinical fields where CAR T cells are used (authorized or in clinical trials), which may evolve as years go by and indications increase\*
- ⊙ Authorities for reimbursements
- ⊙ Clinicians with CAR T cell therapy experience
- ⊙ Referring centers and their hematologists/ oncologists
- ⊙ Patient advocacy groups

\* For example, the Spanish Commissions on CAR T cell Therapy are made up of an *Institutional Commission* that gives final approval to all documents from other committees and groups and makes the final decision regarding CAR T cell center selection, and three *Expert Commissions*: the *Expert Commission to define criteria for designation of centers*, which defines objective criteria and scores to prioritize centers that guarantee safety and equity; the *Expert Commission on the use of CAR drugs at the Spanish National Health System (SNHS) level*, which evaluates guidelines and protocols, and reviews approved indications for CAR T cell therapy in general and for each particular case (ad-hoc subcommittee); and the *Expert commission for optimization of pharmaceutical management related to the use of CAR T cell therapies*, which proposes to the *Institutional Commission* the criteria for sustainable incorporation of CAR T cell therapies.

## 1.6 Ensuring optimal use of CAR T cell therapy

To guarantee the reliability and safety of CAR T cell therapy, definition of the optimal conditions to administer this treatment is mandatory.

Health care professionals from each European Member State that gives marketing authorization for these products will thus need to provide an organizational structure and accreditation for their use. Some European countries such as France and

Spain have already defined the optimal conditions for CAR T cell therapy, and the authors of this manuscript have been involved in the process at the national level.

The main stakeholders involved in the process of CAR T cell therapy are summarized in Box 1.

# REGULATORY FRAMEWORK OF CAR T CELL THERAPY



CAR T cell therapies are included in the regulatory category of ATMPs, within the definition of a gene therapy medicinal product.

In 2009, a specialized committee was created by the EMA: the Committee for Advanced Therapies (CAT) as established in *Regulation (EC) No. 1394/2007 of the European Parliament and of the Council of November 13, 2007, on advanced therapy drugs*. The CAT is responsible for preparing a draft opinion on the quality, safety, and efficacy of CAR T cell therapies for final approval by the CHMP.

*Regulation (EC) No. 1394/2007, on ATMPs*, modifies *Directive 2001/83/EC of the European Parliament and of the Council of November 6, 2001, establishing a community code on medicinal products for human use* and provides for the exclusion of some drugs

from this centralized procedure when they are prepared occasionally, in accordance with specific quality standards, and are used in a Member State at a specific hospital or are intended for a single patient. This is what is known as the hospital exemption clause. The power to authorize medicines under this hospital exemption clause rests on the competent national authorities, through their agencies of medicines and medical devices that establish the traceability and pharmacovigilance requirements of these medicines, once authorized. ATMPs that are prepared on a non-routine basis (such as the manufacture of a custom-made product for an individual patient) and that are not intended to be marketed fall under this hospital exemption clause and are often manufactured directly in (or for) hospitals.

# HOSPITAL REQUISITES FOR CAR T CELL THERAPY

Prior to their transformation into medicines, the human cells from which CAR T cell therapies are derived and their genetic modifications are subject to the national regulations applicable to human cells and tissues for clinical use that result from the transposition of *Directives 2004/23/EC, 2006/17/EC, 2006/86/EC and (EU) 2015/565*<sup>1</sup>.

Provisions of the pediatric regulation are also applicable to ATMPs. The pediatric regulation comprises:

- ☑ [Regulation \(EC\) No 1901/2006](#) of December 2006 on medicinal products for pediatric use;
- ☑ [Regulation \(EC\) No 1902/2006](#), an amending regulation in which changes to the original text were introduced relating to decision procedures for the European Commission.

Member States' legislation linked to these directives needs thus to be considered.

The European Commission takes into account the specificities of ATMPs by means of special regulatory rules for approval, monitoring, and pharmacovigilance. Monitoring and pharmacovigilance are also required by each member

<sup>1</sup> Details listed in Appendix 2

state and pharmaceutical companies. As for other cell therapies, CAR T cell therapies raise concerns for their long-term follow-up. Another important risk-management measure for tisagenlecleucel and axicabtagene ciloleucel is the utilization of a patient registry to monitor the long-term safety and efficacy of these therapies, as a condition of the marketing authorization.

The purpose of registries to support the benefit-risk evaluation of CAR T cell products and their post-authorization follow-up was discussed in a specific workshop in early 2018 as part of the EMA's initiative on patient registries. On March 1, 2019, the EBMT registry was qualified by the EMA as a suitable platform for the collection of data for post-authorization safety surveillance and efficacy studies. The registry is now considered a suitable database for performing pharmaco-epidemiological studies concerning CAR T cell therapy in the treatment of hematological malignancies for regulatory purposes. Therefore, according to this agreement, all consecutive cases of CAR T cell therapy should be reported to the EBMT registry.

Monitoring harmonization or data interoperability is required for the future.

Centers that aim to administer CAR T cells need to guarantee the safety and traceability of the CAR T cell therapy process. The conditions to become a CAR T cell reference center are summarized in Box 2. Other requirements of CAR T cell therapy administration are summarized in Boxes 3 and 4.



## BOX 2: Requirements of CAR T cell therapy centers

### Center selection

Hospitals where CAR-T cell therapy is administered should have the characteristics and experience to guarantee the safety of patients receiving this treatment (further details in Boxes 3 and 4). In the hematology-oncology field, the requirements are similar to those of reference centers for early-phase clinical trials, including novel immune therapies, and/or institutions with an experienced allogeneic HSCT program, particularly from alternative donors and sources.

A functional clinical CAR-T cell unit that integrates multidisciplinary teams experienced in working together to care for intensively treated hematological patients is mandatory.

Hospitals require an on-site clinical hematology unit, with at least one intensive care unit for hematology (ICUH), with access, if necessary, to a protected unit or sector with an operational on-call duty staff member headed by a chief physician. Fast admission to the hospital and the ICUH when necessary must be guaranteed. A well-organized system for specific emergencies as it happens for centers accredited for phase I studies is mandatory. Guidelines and protocols concerning all components of the CAR-T cell therapy process should be in place.

Quality programs and national authorities should accredit the hospital and involved departments. It is highly recommended that the CAR-T cell program is accredited through high-quality procedures such as the Joint Accreditation Committee ISCT-Europe & EBMT (JACIE) for bone marrow transplantation.

Accreditation for a pediatric unit is required for CAR-T cell therapy administration in children. To fulfill the JACIE-FACT standards on immune effector cells therapy is strongly recommended.

The hospital managers should be competent in promoting the CAR-T cell therapy program and giving the necessary resources for its safe development.

### Patient selection

A multidisciplinary committee should evaluate patients who fulfill the criteria for approved CAR-T cell therapies or their inclusion requirements in specific clinical trials. This includes reviewing the diagnosis and indication for treatment as well as evaluating the risk of CAR-T cell therapy. As a minimum, this committee should include specialists in hematology, oncology (depending on hospital organization of clinical care), pediatrics (in case of children and young adolescents), pathology (diagnostic review), intensive care, neurology and eventually immunology and pharmacy (to double check that commercial CARTs are going to be used for an approved indication). Nurses are also important for a whole evaluation of the patient needs. Other health professionals that may be of help in case needed are infectious disease and cardiology specialists, as well as neuroradiologists. It is important that the multidisciplinary committee decision is registered in a CAR-T cell local database. Depending on the Member State's organization, the multidisciplinary committee may be based at each hematology department or CAR-T cell therapy center or at a more regional or national level. The committee should give advice to the patient's hematologist / oncologist / pediatrician

and to the referral center regarding the relevance of CAR-T cell therapy for the patient. Depending on the Member State, the local decision on treatment indication needs to be validated by an external body of experts nominated by national authorities.

### Pharmacy

The pharmacy in a CAR T cell center has an important role in coordinating several aspects of the process once the therapy indication has been established. Participating pharmacists must be accustomed to working in multidisciplinary teams to achieve the best care of patients with severe hematological disorders. Pharmacists must supervise the traceability of the cells from apheresis to infusion, since CAR T cells are considered medicinal products. Pharmacists should also guarantee the availability of all the drugs necessary for CAR T cell therapy and its complications.

### Apheresis

The ability to perform reliable apheresis to obtain T cells for CAR T cell therapy is mandatory. Established apheresis guidelines should always be followed. If the apheresis is to be conducted at a separate facility, communication between the CAR T cell therapy treatment center and the apheresis center needs to be established to coordinate the timing of any mandatory treatment washout periods. It is strongly recommended that the apheresis unit also fulfills national or international standards such as those of JACIE.

### On-site medical laboratory

All CAR T cell therapy centers that prepare CAR T cells need an on-site or reference medical laboratory that can perform various biological quality control tests of the apheresis product, involving hematology, immunology, and bacteriology. Specific on-site biological tests for safety and efficacy monitoring may be required.

### Cell therapy unit

The Cell Therapy Unit consists of the facilities and personnel involved in the reception and processing of the apheresis products, as well as in the preparation of cells before shipping and in many institutions also in the reception of the commercial CAR-T cell products. In these last two steps, pharmacists should be involved since the cells are a medicinal product. More precisely, among other tasks the CTU is necessary to assess the quality of the apheresis product (e.g., number of mononuclear and CD3+ cells, and cell viability). If necessary, an agreement must be made between the CTU and the apheresis unit. In case of academic CARTs the CTU is responsible of the whole process of production under GMP conditions. The CTU usually needs to be authorized by a national body, usually the Ministry of Health. If the cells are for export (i.e., the CAR-T cells are produced outside the hospital in another country), the necessary administrative processing for exit from the country of human biological material should be fulfilled. It is not a requirement that the CTU is on site, but it should be located nearby, within a distance allowing safe transport of the apheresis product in a period shorter than that guaranteeing the quality of the product. The CTU needs demanding quality systems according to national and European standards (e.g., JACIE cell processing and immune effector cells standards).

### T-cell sample transportation prerequisites

Prerequisites for the transportation of T-cell samples and CAR T cells, including traceability of transport, temperature conditions, time periods, and liability, are important whether CAR T cells are prepared on-site or outside the hospital and particularly between:

- ⊙ the apheresis unit and the CTU
- ⊙ the CTU and the hospital before treatment
- ⊙ the CTU and/or pharmacy and the site of CAR T cell production (academic center or manufacturing sites of private companies)
- ⊙ the CTU/pharmacy receiving the processed CAR T cells and the hospital department that will perform therapy (delivery of CAR T cells needs to be under the supervision of a pharmacist).

It should be noted that there are approved transportation companies for blood products and biopharmaceuticals. In terms of liability, the manufacturer is responsible for transport from the CTU to the manufacturer and from the manufacturer to the hospital pharmacy/CTU (routing and delivery of CAR T cells). Requirements for the transportation of hematopoietic stem cells and mononuclear cells (from the sampling site to the CTU) could serve as a basis for the definition of prerequisites for the various stages of transport of patients' cell samples and ATMPs.

#### Reception of CAR T cells

An on-site pharmacy/CTU ensuring the reception of CAR T cells and their storage is needed if a hospital is intending to administer CAR T cell therapy. If the on-site pharmacy does not have the equipment necessary to store CAR T cells (notably, a cryopreservation room), the storage, thawing,

and final packing before administration could, for example, be carried out in a CTU located nearby (at a distance that guarantees the stability of the product during transport). In this situation, an agreement between the on-site pharmacy and the CTU is necessary, it being understood that these steps are under the responsibility of a pharmacist, with the role of each stakeholder clearly specified. The CTU must be authorized for the preservation of autologous mononuclear cells. The organization between the pharmacy/CTU and the possible agreements between them must consider the conditions of use of the CAR T cell therapy used (storage, defrosting, final packaging methods for the administration of the genetically modified ATMP)<sup>2</sup>.

#### Patient preparation for CAR T cell therapy

Whether the manufacturing is in-house or industrial, lympho-depletive chemotherapy must be administered for immunosuppression during the 2 weeks prior to the administration of CAR T cell therapy. Bridging chemotherapy may also be required for patients with aggressive disease. The role of this therapy is to maximize disease control while trying to avoid excessive toxicity that might make the patient ineligible for CAR T cell therapy (including cytopenia-related infections); it does not need to induce a complete response prior to CAR T cell therapy. Bridging therapy may be administered at the referral hospital or at the CAR T cell therapy institution. The multidisciplinary CAR T cell therapy committee must consider these requirements.

<sup>2</sup> For the first two industrially manufactured CAR T cell therapies currently authorized by the European Commission: cryopreservation in nitrogen vapor is necessary before administration; the medication must be injected into the patient within 30 minutes of thawing for tisagenlecleucel (Kymriah®, Novartis) and 3 hours for axicabtagene ciloleucel (Yescarta®, Kite Pharma) to maintain stability. The genetic engineering centers for tisagenlecleucel (Kymriah®, Novartis) are located in New Jersey, USA, and Leipzig, Germany, and that of axicabtagene ciloleucel (Yescarta®, Kite Pharma) is located in California, USA. For both therapies, T-cell samples are frozen in European countries prior to shipment to the USA, specifically Yescarta® in the Netherlands and Kymriah® in Germany.

## BOX 3: Clinical facilities required for safe administration of CAR T cell therapy

**Clinical hematology unit** (inpatient and outpatient). CAR T cell therapy can be administered in a hematology ward, in a hematopoietic transplantation unit, or in a specific CAR T cell patient facility.

**Intensive care unit** with sufficient capacity and staff who are trained in all stages of the use of CAR T cells, from the start of lympho-depletive chemotherapy to completion of therapy.

**Emergency department with on-site medical resuscitation specialists** that guarantees an immediate response when needed.

**Neurology department** on site or able to be rapidly engaged, if necessary. A referral neurologist needs to be appointed to discuss monitoring and care protocols. Performing magnetic resonance imaging (MRI) before baseline initiation could be left to the discretion of the hematologist and/or referral neurologist but is highly recommended for pediatric indications.

#### On-site medical imaging service with MRI.

The full-time (24 hours per day, 7 days per week [24/7]) presence of a professional trained to use the facility's MRI equipment is essential. Performing magnetic resonance imaging (MRI) before initiation of CAR T cell therapy is recommended, particularly for pediatric indications. The hospital should have a radiographic brain MRI patient protocol under CAR T cells (written locally) to allow a radiographer to start MRI in the absence of a radiologist (e.g., at night) without loss of time. An on-site, on-call, radiologist or tele-diagnosis protocol is also highly recommended.

**Pharmacy** available and able to deliver (24/7) all necessary drugs to treat CAR T cell therapy recipients, including those needed for complications of the therapy.

**Transfusion service** able to supply blood components at any time (24/7).

## BOX 4: Human resources needed for CAR T cell therapy

To administer CAR T cell therapy, a center needs medical and paramedical personnel with specific skills. The personnel required are as follows:

- ⊙ **Qualified hematologist/oncologist** or a **pediatrician** who has completed interdisciplinary specialized training (with expertise in cell therapies such as allo- or auto-transplantations; the number of practitioners required may need to be defined). The position of qualified specialist must be covered on-site at all times (24/7). Additional medical staff at the treating department must be trained in CAR T cell therapy to provide support to the qualified specialist. On call hematologist has to be familiar with the on-site well-organized system for specific emergencies (similar to what happens for centers accredited for phase I studies).
- ⊙ **Qualified hematologist/oncologist** or a **pediatrician** who has completed interdisciplinary specialized training (with expertise in cell therapies such as allo- or auto-transplantations; the number of practitioners required may need to be defined). The position of qualified specialist must be covered on-site at all times (24/7). Additional medical staff at the treating department must be trained in CAR T cell therapy to provide support to the qualified specialist. On call hematologist has to be familiar with the on-site well-organized system for specific emergencies (similar to what happens for centers accredited for phase I studies).
- ⊙ **Physicians involved in laboratory diagnosis** (hematology/pathology), **immune studies** (immunology) and **radiology** (particularly neuroradiology).
- ⊙ **Paramedical team**, including state RNs, trained and experienced in the administration of previously cryopreserved cell therapy products and in the management of acute immunological reactions.
- ⊙ **Pharmacist** trained in different aspects of CAR T cell therapy such as the characteristics of the treatment itself, coordination of the process once the T cells are obtained and until CAR T cells are infused, as well as the availability of the drugs required for CAR T cell therapy and its complications.
- ⊙ **Non-medical staff** (biologists, biotechnologists, technicians, and engineers) for CTUs, particularly when academic CAR-T cells are produced on-site.
- ⊙ **Staff trained and responsible for dedicated transportation.** The question of who manages the transport staff will need to be resolved (the sampler or administrator facility, or both), as will the question of whether there is a need for a convention.
- ⊙ **CAR T cell therapy coordinator.** When treatment with CAR T cells is considered, all relevant personnel (including emergency and intensive care doctors, as well as neurologists, pharmacists, immunologists, nurses, and others) must be informed. The coordinator role would be filled by a professional chosen by each center, and would ensure compliance with protocols established for development of the care process. The coordinator may be a physician or another health professional such as a state registered nurse (RN) coordinator.
- ⊙ **Specialists in intensive care, neurology and emergency medicine** with expertise in the multidisciplinary approach of severe complications of hematology/oncology patients and also familiar with the on-site well-organized system for specific emergencies. Access to infectious disease physicians, cardiologists and other specialists when required.

There should be the option of dedicated on-site training, but training courses should also be implemented in each Member State.

# CAR T CELL MANUFACTURING IN THE ACADEMIC SETTING

There are two main systems for clinical CAR T cell production: (a) open systems in bioreactors or other expansion devices for retrovirus, lentivirus gene transfer, or the “sleeping beauty” transposon system method and (b) an automated closed system using the CliniMACS Prodigy (Miltenyi Biotec™). The latter allows cell preparation, enrichment, activation, transduction, expansion, final formulation, and sampling in a single device. Strict GMP conditions are required in the open system of production (levels A and B), whereas an isolation environment is not as necessary for the closed automated device. Despite this, national authorities usually require that the closed process is also performed in GMP facilities, albeit with lower requirement levels (usually level C). Further details on the process of production are described in previous reports<sup>43,44</sup>. In some cases, patients may receive CAR T cells either produced by academia and sent to CAR T cell therapy accredited centers for infusion or CAR T cells produced in-house. Requirements for the in-house production of CAR T cells are summarized in Box 5.



## BOX 5: Hospital settings for CAR T cell therapy production

### In-house CAR T cell production

Non-industrially manufactured ATMPs, including CAR T cell therapies, must meet strict European requirements and guarantees to obtain authorization for use. A CAR T cell therapy manufacturing center authorized under the hospital exemption rule can establish a formal alliance with a network reference center to supply CAR T cells to a group of hospitals. The collaboration agreement must be authorized by the competent authorities at the national and/or regional level.

In-house manufacturing requires

- ⊙ a cell therapy department or CTU with a GMP facility on site or accessible
- ⊙ known/demonstrable activity related to complex cellular processing (umbilical cord blood processing, CD34+ selection, selective T-cell depletion, mesenchymal stromal cell production, etc.), either on site or from a stem cell bank
- ⊙ authorization to perform genetic “*in vitro*” modification using viral vectors and subsequent expansion of modified T cells, and for storing genetically modified cells
- ⊙ accreditation for fulfilling high-quality standards of the facilities and the CAR T cell production process (national, JACIE, others)
- ⊙ Member State authorization for in-house manufacturing of CAR T cells.

# FUTURE DEVELOPMENTS

The CAR T cell therapy field is rapidly evolving. Another CD19 CAR-T therapy is expected to be approved and available on the market soon. Additional indications for CAR T cell treatment are also being investigated, and—in the next few years—patients with multiple myeloma and chronic lymphocytic leukemia may be candidates for this therapy. Novel modalities for CARs are also actively being investigated<sup>1</sup> that could be more efficacious in terms of achieving CR of the disease, extending the persistence of CAR T cells in the recipient, and avoiding relapse as a result of the expansion of malignant cells that do not express the targeted antigen.

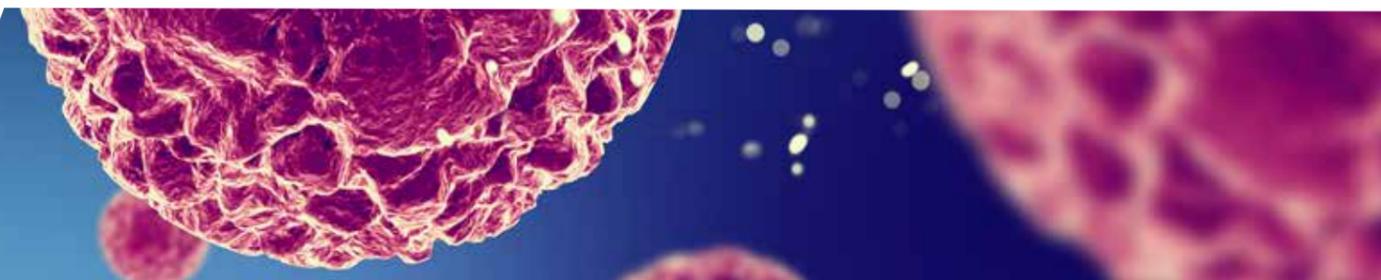
The relevance of the lymphodepleting regimen has recently been emphasized, and adjusting its composition and intensity seems to affect the outcome of CAR T cell therapy<sup>45</sup>.

Development of new approaches to increase the frequency and deepness of responses to CAR-T cell therapy is mandatory. Combining CD19 CAR-T cell therapy with ibrutinib deserves investigation

in patients with relapsed or refractory CLL and eventually other B-cell malignancies. On the other hand preliminary data indicate that PD-1 checkpoint inhibitors may be safely used to improve CAR T-cell persistence.

Also, the recognition and management of toxicities associated with CAR T cell therapy, mainly affecting the lungs and the CNS, is improving. Fractionating the dose of CAR T cells infused and early institution of therapy for complications are becoming accepted strategies, particularly in patients with high tumor burden or more advanced age.

All these developments will increase the safety of CAR T cell therapy, resulting in more patients being treated on a full outpatient basis. The extension of CAR T cell treatment to more cancers, including solid tumors, and the introduction of other immune effector cell therapies such as NK-CARs and tumor infiltrating lymphocytes into clinical practice is expected in the near future.



Universal off-the-shelf allogeneic CAR T cells will become available in the future, and this will necessitate extension of the regulatory aspects herein reviewed, mainly those involving the manufacturing, storage, and delivery of the cells.

All of this will need, on one hand, increased funding from national and European bodies to promote inter-center collaborative academic basic,

translational, and clinical research in this field, and, on the other hand, registration and analysis of clinical outcomes that will allow definition of the best patients to receive CAR T cell therapy. Last, but not least, fair cooperation between academia and companies involved in immune cellular treatments is mandatory for optimal development of this promising yet disruptive advance for patients with malignancies.

## BOX 6: Summary

- ⊙ Chimeric antigen receptor-T cell therapy, or CAR T cell therapy, is a new class of adoptive cellular immunotherapy for cancer treatment.
- ⊙ CAR T cell therapy involves *ex vivo* genetic manipulation of the patient's own T lymphocytes to express the engineered CAR receptor that targets tumor antigens.
- ⊙ More than 492 clinical trials are investigating CAR T cell therapy in the treatment of hematologic or solid cancers around the world.
- ⊙ Stakeholders involved in the definition of the CAR T cell process are:
  - European (EMA) and national authorities for drug authorization (specific for ATMPs)
  - Ministries of Health of the Member States
  - European (EHA) and national societies of hematology, oncology, pediatrics, immunology, and pharmacy
  - European (EBMT) and national societies of hematopoietic transplantation and cell therapy
  - National representatives of clinical fields where CAR T cells are used (authorized or in clinical trials), which may evolve as the years and indications increase
  - Authorities for reimbursements
  - Clinicians with CAR T cell therapy experience
  - Patient advocacy groups.
- ⊙ Tisagenlecleucel (CTL019, Kymriah™) and axicabtagene ciloleucel (KTE-C19, Yescarta™), both directed against the B-lymphocyte antigen CD19, are the first two CAR T cell therapies approved in the USA and Europe; this therapy covers an important medical need in patients with B-ALL and lymphoma.
- ⊙ CAR T cell therapy is associated with potentially severe complications.
- ⊙ To guarantee the reliability and safety of this treatment, definition of the optimal conditions to administer CAR T cell therapy is mandatory.
- ⊙ Health care professionals from each European Member State need to provide an organizational structure and accreditation for the use of CAR T cell therapy.
- ⊙ A multidisciplinary approach that includes specialists additional to hematologists, as well as institutional promotion of the program, are very important requisites.
- ⊙ Immune effector cell therapy for treating cancer is a rapidly evolving field; increased activity because of new indications, and novel strategies and constructs, are expected in the coming years.
- ⊙ Regulatory aspects may need to adapt to novel scenarios.

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## Appendix I

### Spanish Commissions on CAR T cell Therapy

#### 1. Institutional Commission

Gives final approval to all documents from other committees and groups and makes the final decision regarding CAR-T center selection.

Composition:

- ☑ A maximum of two representatives from each of the following:
  - Secretariat-General for Health and Consumer Affairs, Ministry of Health
  - Directorate-General for the Basic Portfolio of Services of the National Health and Pharmacy System, Ministry of Health
  - Spanish Agency of Medicinal Products (AEMPS)
  - National Transplants Organization (ONT)
  - Spanish Institute of Research in Health (Carlos III Health Institute)
- ☑ Six representatives from the Autonomous Communities of Spain (regional governments)
- ☑ Three representatives from patient associations.

#### 2. Expert Commissions

##### 2.1 Expert Commission to define criteria for designation of centers

Defines objective criteria and scores to prioritize centers that guarantee safety and equity.

Composition:

- ☑ One representative from each of the following:
  - Directorate-General for the Basic Portfolio of Services of the National Health and Pharmacy System, Ministry of Health
  - Spanish Agency of Medicinal Products (AEMPS)
  - National Transplants Organization (ONT)
  - Spanish Institute of Research (Carlos III Health Institute)
- ☑ Six representatives from the Autonomous Communities of Spain (regional governments)

- ☑ One representative from each of the scientific societies relevant to this process (Spanish Society of Hematology and Hemotherapy, Spanish Society of Hospital Pharmacy, Spanish Society of Clinical Pharmacology, Spanish Society of Immunology, Spanish Society of Medical Oncology, Spanish Society of Pediatric Hematology and Oncology)
- ☑ One representative from the Cell Therapy Network of Carlos III Health Institute (TERCEL-ISCIH).

##### 2.2 Expert Commission on the use of CAR T cell therapies at the SNH level

To evaluate guidelines and protocols and review approved indications for CAR T cell therapy in general and for each particular case (ad-hoc subcommittee).

Composition:

- ☑ Two individuals representing the Expert Committee on Hematopoietic Stem Cell Transplantation of the Spanish Transplant Organization (ONT) that belongs to the CAR Group of the Spanish Society of Hematology and Hemotherapy (SEHH)
- ☑ One representative from each of the scientific societies relevant to this process (Spanish Society of Hematology and Hemotherapy, Spanish Society of Hospital Pharmacy, Spanish Society of Clinical Pharmacology, Spanish Society of Immunology, Spanish Society of Medical Oncology, Spanish Society of Pediatric Hematology and Oncology)
- ☑ A maximum of six representatives from autonomous communities (regional governments)
- ☑ One representative from the Spanish Bioethics Committee
- ☑ One representative from the Directorate-General for the Basic Portfolio of Services of the National Health and Pharmacy System, Ministry of Health
- ☑ One representative from the Spanish Agency of Medicinal Products (AEMPS)
- ☑ One representative from the National Transplants Organization (ONT).

### 2.3 Expert commission for optimization of pharmaceutical management related to the use of CAR T cell therapies

To propose to the Institutional Commission the criteria for sustainable incorporation of CAR T cell therapies

Composition:

- ☑ Two representatives from
  - Directorate-General for the Basic Portfolio of Services of the National Health and Pharmacy
  - System, Ministry of Health
  - Spanish Agency of Medicinal Products (AEMPS)
- ☑ A maximum of six representatives from autonomous communities (regional governments)
- ☑ Three representatives from the expert group on the use of CAR T cell therapies at the SNHS level.

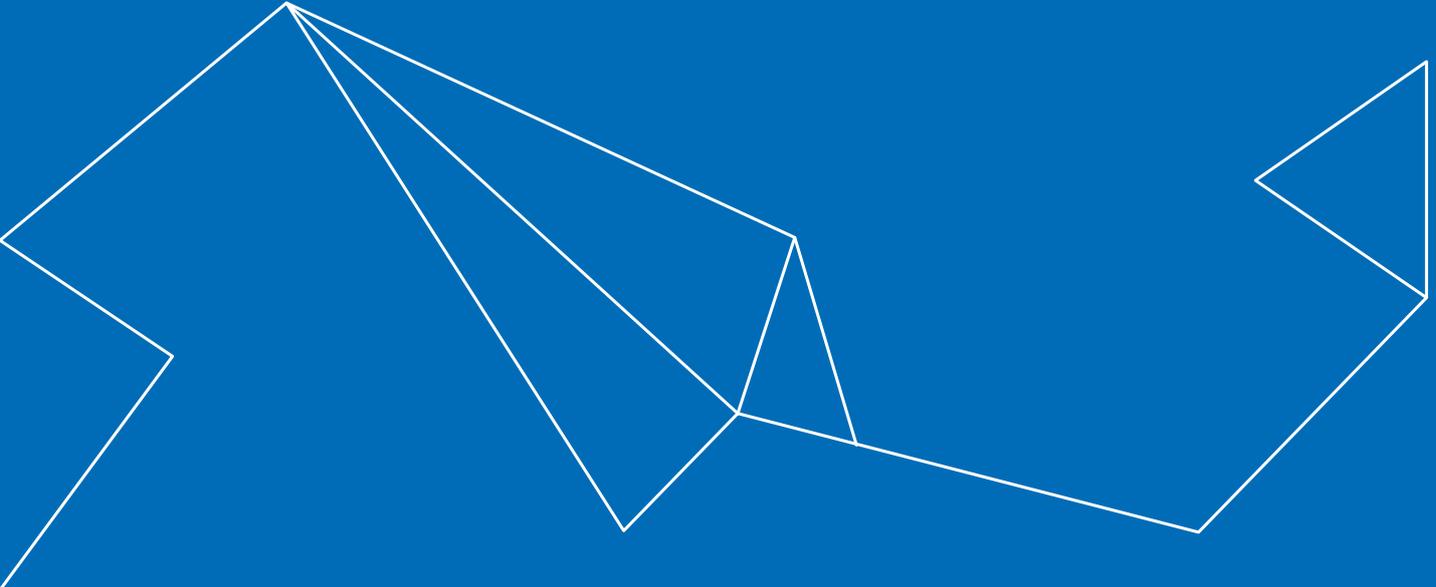
## Appendix 2

### Directives 2004/23/EC, 2006/17/EC, 2006/86/EC and (EU) 2015/565

- ☑ Regulation 1394/2007/EC (ATMP regulation)
- ☑ Directive 2004/23/EC: Definition of standards of quality and safety for the donation, procurement, testing, processing, preservation, storage, and distribution of human tissues and cells
- ☑ Directive 2006/17/EC: (implementing Directive 2004/23/EC regarding technical requirements for the donation, procurement, and testing of human tissues and cells)
- ☑ Directive 2006/86/EC: (implementing Directive 2004/23/EC regarding traceability requirements, notification of serious adverse reactions and events, and certain technical requirements for the coding, processing, preservation, storage, and distribution of human tissues and cells)
- ☑ Directive 2001/83/EC: Community code relating to medicinal products for human use + Annex I
- ☑ Directive 2003/63/EC + in addition to Annex I (regarding ATMP): Directive 2009/120/EC
- ☑ Regulation 726/2004/EC (laying down community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency: Regulation of central authorization of AM)
- ☑ Directive 2001/20/EC and Directive 2005/28/EC (good clinical practice guideline: laying down principles and guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products)
- ☑ Directive 2003/94/EC (good manufacturing practice (GMP) guideline: laying down principles and guidelines of good manufacturing practice with respect to medicinal products for human use and investigational medicinal products for human use)



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