On CAR-Ts, decentralized in-house models, and the hospital exception. Routes for sustainable access to innovative therapies

Luca Arnaudo*†

Italian Medicines Agency - AIFA, Rome, Italy
†Corresponding author. E-mail: lucarnaudo@gmail.com

ABSTRACT
Chimeric Antigen Receptor T cells, or CAR-Ts, are a novel class of gene and cell ‘one-shot’ therapies based upon collecting, reprogramming, and using patients’ own immune cells to treat their cancer. The article discusses the status, prospects, and some relevant legal issues of this frontier of personalized medicine. In particular, it explores the legitimacy of ‘in-house’ CAR-Ts, ie treatments manufactured and delivered to patients within the same clinical center by relying upon automated cell processing systems, a decentralized model which is very different from the one currently adopted for manufacturing existing commercial CAR-Ts. A few legal routes are envisioned for legitimately developing CAR-Ts within decentralized, non-commercial operational sets. In more detail, the article explores, firstly, the issue of ‘academic’ CAR-Ts (ie therapies developed and administered to patients as experimental drugs). A focus is then provided on what is known as the ‘hospital exception’ (HE), a special feature of current EU pharmaceutical regulation for non-routine preparations of custom-made advanced therapy medicinal products. Conclusions support a regulatory convergence on shared...
models of decentralized manufacturing, also through a broader and clearer application of the HE, to enhance a virtuous complementarity between in-house autologous and commercial allogeneic CAR-Ts, for the benefit of patients, pharmaceutical R&D, and sustainable healthcare systems.

**KEYWORDS:** ATMP, CAR-T, CGTP, decentralized manufacturing, hospital exception

I. INTRODUCTION
When moving along a frontier, conditions and rules are usually uncertain. The first explorers often act as improvised legislators with varying intentions and abilities, creating more or less welcoming outposts for those who follow. This feeling applies to the classification and regulation of a particular kind of innovative immunotherapies at the forefront of both regenerative and genomic-driven personalized medicine: Chimeric Antigen Receptor T cells, or CAR-Ts, successfully deployed in the past few years for treating some severe forms of blood tumors, with application fields growing exponentially.

This article addresses a series of unmet academic and practical needs. It provides a primer on CAR-Ts, the ways they are currently administered to patients, related costs, and looming therapeutic perspectives. There is a need for such an integrated introduction to a broader audience, as analyses have so far been confined to medical-scientific publications in a scattered way. It then connects legal and technical dots for supporting and further developing a trend recently observed in some economically advanced countries, ie the establishment of hospital networks where advanced therapies can be manufactured and administered ‘in-house’ on a decentralized basis. The increasing availability of automated cell processing systems is being leveraged by clinical centers around the world for developing new CAR-Ts, possibly with same safety guarantees, higher efficacy, and at lower costs than the products commercially distributed so far.

As for its structure, the article will provide a summary of the state of CAR-Ts scientific research and expected developments (Part II), introducing current decentralized in-house practices (Part II.A.1). An analysis of US and EU applicable regulatory frameworks will follow (Parts III and IV), with a focus on two already established paths for decentralized in-house CAR-Ts, namely ‘academic’ experimental drugs manufactured and administered through clinical trials (Part IV.A), and an ‘hospital exception’ (HE) that, according to existing EU provisions, allows non-routine preparations of custom-made advanced therapy medicinal products outside a clinical trial setting (Part IV.B). Considering the above, conclusions will support the consolidation and a broader application of rules, such as the EU HE, in view of further developing decentralized in-house CAR-Ts on a legally and economically sustainable basis (Part V). By doing so, it is argued that there is hope to guarantee broader access to new treatments that are re-shaping many of the current therapeutic standards.

II. A PRIMER ON CAR-T CELL THERAPIES
The acronym CAR-T corresponds to ‘Chimeric Antigen Receptor T cell’ and refers to a class of gene and cell therapies based on a process of engineering T lymphocytes, a type of white blood cells (leukocytes) that is an essential part of the immune system. After being collected through a blood sample from the patient (leukapheresis), T cells are genetically modified and ‘reprogrammed’ by using specific viral vectors to express
receptors of an antigen; once reinfused into the patient, they can become a persistent cell population able to recognize an attack, bind to the tumoral cells, and eliminate them.\(^1\) As for the **chimeric** of the term, it refers to the fact that both the binding function of the antigen and that of activating T lymphocytes are combined in a single receptor: by means of this manipulation cells are ‘armed’ for targeted immunological response.

We can thus speak of ‘samurai cells’ which, after having been trained, will loyally serve their lord. The metaphor only applies to the **autologous** CAR-T currently available on the market; this term referring to therapies developed by modifying cells of the same subject in which they will be reinfused. However, ongoing trials are also testing therapies based on modified cells of donors (via CRISPR/Cas9 gene-editing\(^2\)) other than the patient, known as **allogeneic** CAR-Ts. The opportunities attached to allogeneic therapies are extremely relevant, as they could allow for treatments based upon ‘ninja cells’, just to keep the belligerent quip, because of their availability to fight as mercenaries to hire. In fact, allogeneic CAR-Ts would be ready ‘off-the-shelf’,\(^3\) with evident optimizations in terms of production and administration.

CAR-Ts are based upon research launched in the early 1990s and were successfully used on humans for the first time at the beginning of the 2010s in the USA as experimental treatments to be administered within a clinical trial framework.\(^4\) The first commercial version of a CAR-T was marketed in the USA in August 2017 and in the EU in June 2018.\(^5\) As we will see in more detail in the next section, a handful of autologous CAR-T is currently available for the treatment of some serious blood tumors, most notably B-cell acute lymphoblastic leukemia, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, and multiple myeloma. Because of their highly experimental features, CAR-Ts have been initially used as third-line treatments (meaning that two previous rounds of standards of care, such as chemotherapy and radiotherapy, did not produce positive effects), and only in pediatric patients and young adults up to age 25. However, these therapies are increasingly applied also for treating adults, at least for certain blood tumors, with remarkable results: percentages of complete remission, depending on the pathology, have been reported to be higher than 70 per cent.\(^6\)

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1. Medical-scientific literature on the subject is growing exponentially; for a clear introduction, see, among many others, Robert C. Sterner & Rosalie M. Sterner, *CAR-T Cell Therapy: Current Limitations and Potential Strategies*, 11 Blood Cancer J 1–11 (2021); see also Rebecca Larson & Marcela Maus, *Recent Advances and Discoveries in the Mechanisms and Functions of CAR T Cells*, 21 Nat Rev Cancer 145–161 (2021).

2. For an introduction about how to ‘crispr’ human T cells, see Bettina Bernard et al., *CRISPR/Cas-based Human T Cell Engineering: Basic Research and Clinical Application*, 245 Immunol. Lett. 18–28 (2022).

3. Blake Aftab et al., *Toward 'Off-the-Shelf' Allogeneic CAR T Cells*, 3 ADVANCES IN CELL AND GENE THERAPY 1–11 (2020), see also Ehsan Razeghian et al., *A Deep Insight into CRISPR/Cas9 Application in CAR-T Cell-Based Tumor Immunotherapies*, 12 STEM CELL RES THER 1–17 (2021).

4. Carl June et al., *CAR T Cell Immunotherapy for Human Cancer*, 359 Science 1361–1365 (2018); for an anecdotal account of the beginnings, see Lisa Rosenbaum, *Tragedy, Perseverance, and Chance—The Story of CAR-T Therapy*, 317 New Engl. J Med 1313–1315 (2017).

5. FDA, *FDA Approval Brings First Gene Therapy to the United States*, press release, August 30, 2017; see also Asher Mullard, *FDA Approves First CAR T Therapy*, 16 Nat Rev Drug Discov 669 (2017). As for the EU, see EMA, *First Two CAR-T Cell Medicines Recommended for Approval in the European Union*, press release, June 29, 2018.

6. Katherine Harris, James LaBelle & Michael Bishop, *Current Status of CAR T Cell Therapy for Leukemias*, 22 Curr Treat Option On 1–17 (2021).
Relevant difficulties persist in avoiding or mastering serious adverse reactions, such as cytokine release syndrome and neurotoxicity; tumor relapses have also been registered. Moreover, apart from some very recent reports on two early recipients of CAR-Ts who remain cancer-free a decade later, the novelty of these therapies still does not allow to rely upon long-term data about complete response rates. This informational limit is further coupled with the usual scarcity, if not plain absence, of comparative clinical trials. Hopes are high, however, to overcome most of the limits indicated above, supporting a continuous expansion of therapeutic applications by targeting both new diseases and diverse types of patients. A brief review of some ongoing lines of research can provide clues about looming bright perspectives.

As of the writing of this article (mid-of-year 2022), several experimentations of allogeneic CAR-Ts for the treatment of solid tumors have been authorized, pointing toward the possibility of moving beyond current applications limited to liquid tumors and also to rely upon an off-the-shelf production. Furthermore, recent studies proved the possibility to use CAR-Ts for treating autoimmune diseases, such as lupus, and, in combination with mRNA applications, widespread cardiac injuries, such as fibrosis. Preliminary clinical trial results support the idea of leveraging the ‘new wave’ of mRNA-driven vaccines for combining them as boosters for CAR-Ts anti-cancer treatments. Under a broader viewpoint, several clinical trials have been launched for testing the chimerization of receptors antigens to lymphocytes of the immune system other than T cells, most notably the large granular lymphocytes (so-called ‘Natural Killers,’ or NK cells) that play a critical role in eliminating tumor and virus-infected cells. Should this path prove to be practicable, it will then be possible to refer to CARs (instead of CAR-Ts) as a broader vehicle for developing immunotherapies.

As we will see in more detail, however, new therapies came at a cost.

II.A. Current Costs and New Organizational Models of CAR-Ts

So far, six CAR-T therapies have been approved for commercial use by the most important regulators on a worldwide basis, notably the US Food and Drug Administration.
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... (FDA) and the European Medicines Agency (EMA). These products, usually identified as ‘commercial CAR-Ts’ because of the marketing authorization path that followed, are tisa-cel (marketed under the proprietary name Kymriah™ by Novartis), axi-cel (Yescarta™, Kite-Gilead), brexu-cel (Tecartus™, Kite-Gilead), ide-cel (Abecea™, BMS-Bluebird), liso-cel (Breyanzi™, BMS-Juno), and cilta-cel (Carvykti™, J&J-Legend). The last two CAR-Ts have been authorized very recently, in the first half of year 2022, while a seventh CAR-T, relma-cel (JW Therapeutics), obtained a special approval valid in China only. Along with the currently marketed therapies, updated surveys provide a clear demonstration of the impressive CAR-Ts R&D pipeline near to marketing applications: according to a horizon scanning survey from the end of 2021, ten CAR-Ts clinical trials have been reported to be in phase III, while hundreds of clinical trials are currently in phase II and I, with USA and Chinese institutions currently leading the research race.

It is important to note that CAR-Ts are ‘one-shot’ therapies, i.e., they can treat target diseases by means of a single treatment, thus sparing (when successful) the persistent costs attached to chronicization. However, apart from the high extra expenses related to side-effects management, the cost-effectiveness of these novel therapies has been recurrently questioned when considering their prices.

All the CAR-Ts marketed so far show price tags in the order of several hundred thousand dollars for a single infusion: the first CAR-T ever approved was introduced on the US market at a price of $475,000, with newcomers swiftly aligning to similar price levels. Various studies pointed to the need for these therapies to substantially increase overall survival versus current standards of care to become sustainable vis-à-vis the existing cures, based on a measurable way of health outcome gained (such as by Quality Adjusted Life Years, QALYs). As already mentioned, however, the novelty of the CAR-T therapies makes difficult to rely upon follow-up studies on a sufficiently ample basis.

In view of managing current uncertainties about therapeutic efficacy and the financial impact of CAR-Ts, as well as to better adapt to their special features (e.g., being one-shot therapies), advanced healthcare systems have embraced the use of innovative...
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negotiation schemes (such as Management Entry Agreements, MAEs) centered on pay-for-result or pay-at-result models.\(^{20}\) Such contracting paths are promising, also as a possible testbed for wider applications to different new pharmaceutical products; however, they raise unprecedented technical difficulties and administrative hurdles, such as the need to establish updated registries and dynamic monitoring activities.\(^{21}\) MAEs, either purely financial or performance-based, are solutions pursued under the current cost pressure of commercial CAR-Ts, in a clear attempt to dilute their economic burden by better relating the prices to the therapeutic results obtained over a longer period. Indeed, since the first launch of these novel therapies, their prices caused persistent and widespread worries about the same sustainability of healthcare systems of high-income countries, with access issues for the rest of the world being even more critical.\(^{22}\) The current level of costs has also been considered the main obstacle to the use of such therapies in the early stages of tumoral diseases.\(^{23}\)

II.A.1. Decentralized Point-of-Care Models

Apart from these economic side-effects, the limits of the current industrial model of commercial CAR-Ts are becoming increasingly evident. This model is centered on manufacturing activities concentrated in the very few centers operated by the pharmaceutical companies holding the relevant marketing authorizations. Because cell manufacturing occurs at great distances from the hospitals in which the therapy based upon that specific CAR-T is in progress, there is a need to freeze and thaw the cells for moving them back and forth, a process that might impact the therapeutic efficacy.\(^{24}\) On the top of that, complex issues with patient access logistics also arise.\(^{25}\)

Alternatively, specialized manufacturing sites placed as close as possible to the patients facilitate production and administration efficiencies, first of all the timely availability of ‘fresh’ cells, without having to resort to cryogenization, thus drastically

\(^{20}\) Martin Wenzl & Suzannah Chapman, *Performance-Based Managed Entry Agreements for New Medicines in OECD Countries and EU Member States: How They Work and Possible Improvements Going Forward*, OECD Health Working Papers, no. 115 (2019). For a general survey of the first CAR-T-related MAEs, see Jesper Jørgensen, Eve Hanna & Panos Kefalas, *Outcomes-Based Reimbursement for Gene Therapies in Practice: The Experience of Recently Launched CAR-T Cell Therapies in Major European Countries*, 8 J MARK ACCESS HEALTH POLICY 1–13 (2020).

\(^{21}\) For a practical case-study, see Entela Xoxi, Karen M Facey & Americo Cicchetti, *The Evolution of AIFA Registries to Support Managed Entry Agreements for Orphan Medicinal Products in Italy*, 12 FRONT PHARMACOL (2021).

\(^{22}\) The tone was set by the same title of an early commentary: Christian Chabannon et al., *CAR-T Cells: The Narrow Path Between Hope and Bankruptcy?* 52 BONE MARROW TRANSPL 1588–1589 (2017). For a view from low- and middle-income countries, see, more recently, Kenneth Cornetta et al., *Gene Therapy Access: Global Challenges, Opportunities, and Views from Brazil, South Africa, and India*, 30 MOL. THER. 1–8 (2022).

\(^{23}\) Drew Amorosi, *Earlier CAR-T Treatment Possible if Price comes Down*, FDA Official Says, HEMONC TODAY, October 28, 2021 (https://www.healio.com/news/hematology-oncology/20211028/earlier-cart-treatment-possible-if-price-comes-down-fda-official-says, accessed Aug. 1, 2022).

\(^{24}\) ‘Cryopreservation of the apheresis product after collection can also influence cell quantity and quality’ (Mohamed Abou-el-Enein et al., *Scalable Manufacturing of CAR T Cells for Cancer Immunotherapy*, 2 BLOOD CANCER DISCOV 408–422, 409 (2021)).

\(^{25}\) Annette Hay & Matthew Cheung, *CAR-T-Cells: Costs, Comparisons, and Commentary*, 22 J MED ECON 613–615 (2019). For interesting considerations related to the set-up in progress of the required infrastructures, see Joel Wayment, *CAR-T Therapies: Three Supply Chain Considerations*, 17 PHARMACEUTICAL COMMERCE 27–29 (2022).
speeding up the ‘needle-to-needle’ therapeutic process (leukapheresis, cells reprogramming, reinfusion). This is why new licensing procedures have been proposed to allow multiple manufacturers to use a common protocol.\textsuperscript{26} Advantages of decentralized or ‘redistributed manufacturing’ have already been highlighted by other commentators also in view of ‘democratising supply, creating jobs without geographical restriction to the central hub and allowing a more flexible response to external pressures and demands’.\textsuperscript{27}

This paradigm shift is possible because of important technological advances that took place with respect to the manipulative cycles of human cells necessary for developing advanced therapies, such as CAR-Ts, thereby allowing unprecedented decentralization of manufacturing activities. The increasing availability of closed, semi-automated or even fully automated manufacturing systems, able to process the whole-cell treatment cycle under controlled conditions, now allows also small organizational entities to meet the high standards dictated by applicable regulations of Good Manufacturing Practices (GMPs),\textsuperscript{28} pursuing an effective quality-by-design approach.\textsuperscript{29} More recently, technological innovation is following the path of easily scalable manufacturing platforms by relying upon movable on-site cell labs provided by specialized companies focused on a point-of-care business model, with complex service agreements aimed at covering various operational needs, from trained personnel to interchangeable equipment supplies.\textsuperscript{30}

The organization of decentralized production of new advanced therapies, such as CAR-Ts, certainly presents difficulties. At the same time, as other studies have noted, decentralized systems for other types of therapies can be taken as a reference,\textsuperscript{31} even more so in national health systems where networks of hospital centers already exist.

An explicit attempt to address the economic concerns raised by the commercial CAR-T developments by leveraging the new possibilities of decentralized manufacturing is underway with several healthcare systems moving toward the establishment

\textsuperscript{26} Cf. Peter Marks & Scott Gottlieb, \textit{Balancing Safety and Innovation for Cell-Based Regenerative Medicine}, 378 \textit{NEW ENGL J MED} 954–959 (2018).

\textsuperscript{27} Richard Harrison et al., \textit{Decentralised Manufacturing of Cell and Gene Therapy Products: Learning from Other Healthcare Sectors}, 36 \textit{BIOTECHNOL ADV} 345 (2018).

\textsuperscript{28} According to a report commissioned by the Austrian government, ‘several countries are exploring an alternative decentralized CAR T-cell production mode (“in-house/point-of-care CAR T-cell production”), e.g. based on the use of CliniMACS Prodigy, a semi-automated closed system by Miltenyi Biotech. Several clinical trials are currently underway to investigate this manufacturing process’ (Sabine Geiger-Gritsch et al., \textit{CAR T-Cell Therapy. Horizon Scanning}, EBEU REPORT 11/2020; 42 (2020)).

\textsuperscript{29} ‘… considerable variability can hinder CAR T cell manufacturing. While variable gene expression is unavoidable in current CAR T cell generation protocols owing to retro- and lentiviral vector integration, variabilities in other manufacturing parameters can be better controlled by adopting “Quality by Design” (QBD) principles. QBD principles evaluate theoretical variabilities in a process and assess risk to detect which critical parameters need to be kept under tight control.’ (Mohamed Abou-el-Enein et al., \textit{supra} note 24 at 416).

\textsuperscript{30} Vivienne Raper, \textit{Precision Medicines That Are Tailored and Off-the-Rack}, 40 \textit{GENET ENG BIOTECHN} N epub (2020).

\textsuperscript{31} ‘Useful paradigms include the manufacture of radioisotopes for nuclear medicine, personally-titrated anti-cancer agents, total parenteral nutrition (TPN) products and blood and platelet supplies. The essential, identifiable attributes of decentralised manufacturing are: responsiveness to evolving requirements, personalisation to patient requirements as well as aseptic manufacture, shipping and release’ (Richard Harrison et al, \textit{supra} note 27, at 346).
of hospital networks for the production and administration of so-called ‘in-house’ CAR-Ts. In essence, the goal is a point-of-care-based manufacturing and management model. This model aims at leveraging, on one hand, the existence of research activities of academic centers of excellence already integrated into hospitals and, on the other hand, the unprecedented accessibility of automated cell labs mentioned above; in this perspective, it is possible to imagine an hub and spoke model centered on a few research and production nodes of excellence connected to a series of other hospitals located at a distance that maintains the advantages of a CAR-T ‘fresh’ manufacturing and administration, thus allowing the distribution of advanced therapies in a more widespread way and avoiding the movement of patients in often critical conditions.

The first economic estimates related to in-house CAR-Ts already manufactured and delivered in EU hospitals show final costs for each CAR-T therapy significantly lower than those of the commercial ones. According to various scenarios, such costs vary between 35,000 and 60,000 euros. In all probability, economic burdens will decrease further thanks to technological and scientific developments currently in progress.

In order to secure the practical viability of the in-house path outlined above, it is now important to verify and secure its legal sustainability. This is a task that requires an answer to interesting preliminary questions, starting with the very nature of CAR-Ts as medicine products.

### III. CAR-TS REGULATION AND GOVERNANCE

CAR-Ts are fully integrated in the regenerative medicine, an emerging interdisciplinary field aiming to replace or regenerate human cells, tissues, or organs to restore or establish normal functions. Because of their ability to target malignancies within a single patient, these therapies are also the epitome of genetic-driven personalized medicine, another trend of broad scope in contemporary medicine. Where to exactly place CAR-Ts from a stricter regulatory viewpoint, however, is a different issue.

When CAR-Ts were first unveiled, discussions arose regarding how to consider them; because of their biological sources, manufacturing processes, and therapeutic design, there were doubts about the legitimacy to consider CAR-Ts as drugs instead of methods of medical treatment. Legal and economic consequences of this distinction were enormous, as many countries around the world forbid the patenting of methods of medical treatment. Even where this is allowed, such as in the USA, the scope of patenting and related enforcement are much narrower than for other medicines. Also, only drugs require premarket approvals by regulatory agencies.

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32 Tao Ran et al., Cost of Decentralized CAR T-Cell Production in an Academic Nonprofit Setting, 12 Int J Cancer 3438–3445 (2020).
33 Tingting Qiu et al., Regenerative Medicine Regulatory Policies: A Systematic Review and International Comparison, 124 Health Policy 701 (2020).
34 ‘Genetic research has opened up frontiers previously unexplored, which provide opportunities for medical breakthroughs, commercialization, and personal understanding’ (Shubha Ghosh, Identity, Invention, and the Culture of Personalized Medicine Patenting 214 (2012)).
35 Louis Abinander & Jorge Contreras, The Patentability of Genetic Therapies: CAR-T and Medical Treatment Exclusions Around the World. 34 AM UNIV INT LAW REV 708 (2019). In this regard, it should be remembered that the World Medical Association has adopted a formal declaration on the patentability of medical procedures with which it has clearly raised a question of ethical legitimacy of the same. The declaration, adopted in 1999, was reaffirmed in 2019 (cf. WMA, Statement on Patenting Medical Procedures, Santiago del Chile, May 3, 2019).
with a profound impact on products’ R&D processes, expectations, costs—and prices.

After initial uncertainties, the patenting of CAR-T inventions has increased exponentially since 2013.\textsuperscript{36} This trend proved to be commercially far-sighted. Notwithstanding, some important jurisdictions, such as the EU, formally adopted ‘a new, third category . . . to bridge the gap between medical devices and medicinal products’,\textsuperscript{37} CAR-Ts were eventually included in the ‘drug paradigm’,\textsuperscript{38} with a consequent application of both regulatory and patent frameworks applied to medicinal products. This framework ensures quality, safety, efficacy, and marketing exclusivities. Such a move was part of an extensive regulatory process aimed at supporting a pharmaceutical assessment for the growing number of new biological Advanced Therapy Medicinal Products (ATMPs) based on human gene, cell, and/or tissue engineering, in their turn to be included in the broader category of Cell, Gene, and Tissue Therapy Products (CGTPs).\textsuperscript{39}

In fact, CGTPs encompass both ATMPs, now covered by regulatory standards for drugs, and cell and/or tissue-based therapies subject to non-pharmaceutical blood or transplant laws. In the USA, human cells, tissues, and cellular- and tissue-based products, ie CGTPs, are labeled as HCT/Ps, while in the EU, according to current regulation, a further regulatory distinction within CGTPs exists between Gene Therapy Medicinal Products and somatic Cell Therapy Medicinal Products (GTMPs and sCTMPs, respectively).

In December 2021, the World Health Organization (WHO) issued a document aimed at establishing a regulatory convergence among the most advanced legal and pharmaceutical ecosystems.\textsuperscript{40} Some differences in sub-classifications do persist between the USA and the EU: both regulatory systems, however, agreed on the need to refer to the level of modification occurring to cell materials in order to assess the ATMP nature of a CGTP.\textsuperscript{41}

\section*{III.A. Current US and EU Regulatory Frameworks for Advanced Therapies}

In the USA, a fundamental distinction occurs between CGTPs that fall either under section 351 (drugs) or section 361 (non-drugs) of the Public Health Services Act (PHSA), based upon the criteria set by title 21 of the Code of Federal Regulations

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\bibitem{36} Louis Abinander & Jorge Contreras, \textit{supra} note 35 at 718–721. See also Björn Jürgens & Nigel Clarke, \textit{Evolution of CAR T-Cell Immunotherapy in Terms of Patenting Activity}, 37 \textit{Nat Biotechnol} 370 (2019).
\bibitem{37} Miranda Mourby et al., \textit{Biomodifying the ‘Natural’: from Adaptive Regulation to Adaptive Societal Governance}, 9 \textit{J. Law & Biosciences} 14 (2022).
\bibitem{38} Rohan Chalasani, Tina Hershey & Walid Gellad, \textit{Cost and Access Implications of Defining CAR-T Therapy as a Drug}, 1 \textit{JAMA Health Forum} 1 (2020).
\bibitem{39} The origins of this process can be traced back to a 1997 FDA document aimed at introducing a ‘tiered risk-based approach’ to regulate and classify human cell and tissue-based products (cf. Mark Lee et al., \textit{Overview of the FDA Regulatory Process, in ESSENTIALS OF STEM CELL BIOLOGY} 614 (Robert Lanza and Anthony Atala eds., 2014)).
\bibitem{40} WHO \textit{Considerations on Regulatory Convergence of Cell and Gene Therapy Products}, working paper, WHO/CGTPs/DRAFT/16 December 2021.
\bibitem{41} For a general reconstruction, see Carolina Iglesias-Lopez et al., \textit{Regulatory Framework for Advanced Therapy Medicinal Products in Europe and United States}, 10 \textit{Front Pharmac} 1–14 (2019). For a focus on the US regime only, confirming the general idea that ‘regulatory framework is risk-based,’ cf. Peter Marks & Scott Gottlieb, \textit{supra} note 26, at 955.
\end{thebibliography}
(CFR) part 1271. Specifically, according to 21 CFR 1271.10(a)(1), a ‘human cells, tissues, and cellular and tissue-based product’ is regulated solely under section 361 if it is ‘minimally manipulated’, interpreted by the FDA as ‘processing that does not alter the relevant biological characteristics of cells or tissues’. Furthermore, to fall under section 361 of the PHSA a CGTP must be intended ‘for homologous use only’, i.e. ‘the repair, reconstruction, replacement, or supplementation of a recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor’. This definition implies, \textit{a contrario}, that a section 351 product must undergo a substantial manipulation of the cell material and be used for performing different functions than the original ones. A CGTP (more specifically, an HCT/P) falling under section 351 is a biologic product, thereby bound to follow the stringent Biologics License Application process in order to be introduced, or delivered for introduction, into interstate commerce according to 21 CFR 601.2. In the aftermath of the 21st Century Cures Act, signed into law on December 13, 2016, the FDA implemented section 3033 of the act by defining a new special status of ‘Regenerative Medicine Advanced Therapy’ (RMAT) that can be recognized to section 351 products in view of granting a more expedited regulatory evaluation and approval, thus creating a new product label to be possibly applied to innovative new drugs.

As for the EU, normative and interpretative principles currently align with the ones established in the USA. Article 2(1)(c) of Regulation 1394/2007/EC establishes that, in order to consider modified cells or tissues as ATMPs, they must have been subject to ‘substantial manipulation, so that the biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved’, and/or such materials ‘are not intended to be used for the same essential function or functions in the recipient as in the donor.’ The definition further combines with Annex 1 of the same Regulation 1394/2007/EC, which provides a list of explicitly non-substantial manipulations. As for their approval, a relevant role is played by a scheme called PRIME, launched in 2016 by the EMA for accelerating the development and approval of promising products targeting conditions with high unmet medical needs.

For the sake of completeness, it must be said that the current EU legislative framework for medicines is expected to be revised, following an ambitious strategy adopted by the EU Commission at the end of year 2020, with recurring news about incoming ‘flagship initiatives’ of regulatory reforms. Most likely, however, the sub-set of rules

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\item FDA, \textit{Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff}, 4 (July 2020).
\item Id.
\item Annegret Vaggelas & Diane Seimetz, \textit{Expediting Drug Development: FDA’s New Regenerative Medicine Advanced Therapy Designation}, 53 \textit{Ther Innov Regul Sci} 364–373 (2019).
\item Such non-substantial manipulations include cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification.
\item For a first evaluation, see Asher Mullard, \textit{PRIME Time at the EMA}, 32 \textit{Nat Rev Drug Discov} (2017).
\item The reform process can be followed through the official webpage of the EU Commission, \textit{A pharmaceutical strategy for Europe}, and related documents (https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe_en#latest-updates, accessed Aug. 1, 2022).
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directly affecting ATMPs will maintain its core elements, starting from the regulatory definitions discussed in this section.

III.B. Philosophical Hurdles and Regulatory Perspectives
Amid the tangle of provisions, acronyms, and distinctions outlined in previous sections, the assessment of the specific nature of CAR-Ts is made complex by their being both a gene and a cell therapy—as well as (at least so far) an autologous process most likely similar to a transplant. It is no wonder, then, that CAR-Ts have already been considered a ‘philosophically difficult therapy’. Metaphysics aside, substantial manipulation and non-homologous use certainly occur during the CAR-T manufacturing, as T cells (as explained in Part II of this article) are genetically reprogrammed and equipped with new functionalities in view of targeting, connecting, and eliminating malign cells.

Regulators embraced this view. In fact, when considering the CAR-Ts marketing authorizations granted so far, both in the USA and the EU, it can be safely considered res judicata that such products are at the same time CGTPs, and ATMPs, in the USA, more specifically, these products fall under the category of Section 351 biologic products and the sub-category of regenerative therapies in view of the RMAT status recognition. Also, because of the small numbers of the population affected by the diseases targeted by the products currently marketed, it is worth noting that all commercial CAR-Ts in the USA and the EU obtained an orphan drug designation.

Once this reference grid has been defined—with CAR-Ts, at least according to existing regulatory scenarios, well-entrenched among drugs—it is finally possible to consider which are the legitimate production and administration routes of in-house CAR-Ts, focusing on a specific provision of existing EU legal framework that shows high compatibility with the envisioned trend toward decentralized point-of-care manufacturing and administering of advanced cell and gene therapies.

IV. LEGAL ROUTES FOR IN-HOUSE CAR-TS
Because of their pharmaceutical status, CAR-Ts aimed at being marketed follow the well-established path of pre-market approvals by regulatory medicines authorities, with consequent recognition of exclusive rights to Marketing Authorization Holders (MAHs), most often the owners or licensees of the product’s intellectual property rights.

This conventional path has little relevance in the perspective of decentralized in-house CAR-Ts, such as the one envisaged in part II.A, as the costs related to regulatory assessments would be prohibitive and make non-commercial projects economically unsustainable. The MAH of a commercial CAR-Ts may decide to voluntarily license the manufacturing of their products to point-of-care cell labs networks, given a shared

48 Jacob Sherkow, Patricia Zettler & Henry Greely, Is It ‘Gene Therapy’? 5 J. LAW & BIOSCIENCES 792 (2018).
49 Cf. supra note 5. For a broader view, cf. Delphi Coppens et al., A Decade of Marketing Approval of Gene and Cell-Based Therapies in the United States, European Union and Japan: An Evaluation of Regulatory Decision-Making, 20 CYTOTherapy 769–778 (2018).
50 For an introduction to this path, and to the way CAR-Ts are following it, see Misty Attwood, Mathias Rask-Andersen & Helgi Schiöth, Orphan Drugs and Their Impact on Pharmaceutical Development, 39 TRENDS PHARMACOL SCI 525–534 (2018).
51 Giulia Detela & Anthony Lodge, EU Regulatory Pathways for ATMPs: Standard, Accelerated and Adaptive Pathways to Marketing Authorisation, 13 MOL THER—METHODS CLIN DEV 205–232 (2019).
greater economic utility and therapeutic efficacy of production activities close to the patients: it is clear, however, that other paths prove much more interesting for the establishment of decentralized in-house systems. In the following sections, two legal routes will be explored, namely so-called academic CAR-Ts, and a special feature of EU existing regulatory framework known as HE.

IV.A. In-House CAR-Ts as Experimental Drugs: The Academic Way

Every major regulatory environment foresees a discipline for experimental drugs. These are chemical or biological substances whose efficacy and safety are yet to be fully verified and validated for pharmaceutical uses. When approved by competent authorities (eg medicines agencies and independent ethics committees), they can be tested on humans through rounds of clinical trials. According to some special provisions aimed at providing expanded access, such as the recently approved US ‘Right-to-Try’ Act, experimental treatments can be administered even outside of clinical trials to patients with life-threatening diseases. As a general criterion, experimental drugs neither be advertised or sold nor prescribed according to usual procedures. Also, regulatory oversight does exist, but rules related to ordinary pharmaceutical issues, such as product labeling and nomenclature, are much more scattered and scantier than usual (for instance, an experimental drug is usually identified by simply using a number combined with an abbreviation of the sponsoring company’s name, like a vehicle’s license plate).

Experimental drugs are technically referred to as Investigational New Drugs (INDs) in the USA and as Investigational Medicinal Products (IMPs) in the EU. According to 21 CFR, part 312.3(b), an IND ‘means a new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes’. In its turn, Regulation EU/536/214, article 2(5), established that an IMP ‘means a medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial’, further specifying for ATMPs, in a rather tautological way, that ‘Advanced therapy investigational medicinal product’ means an investigational medicinal product which is an advanced therapy medicinal product as defined in point (a) of Article 2(1) of Regulation (EC) No 1394/2007’ (article 2(7)).

Many hospitals and research centers around the world have been relying for years on investigational CAR-Ts to respond to unmet medical needs, within the safety framework provided by clinical trials. The growing availability of decentralized point-of-care systems is now finely matching this trend: these products are usually known as ‘academic’ CAR-Ts, because of their link with clinical centers of excellence and related research activities.

52 The administration of experimental drugs raises important and complex ethical questions: for an updated consideration of the topic, with some interesting operational proposals, see Jan Borysowski & Andrzej Gorski, Ethics Framework for Treatment Use of Investigational Drugs, 21 BMC MED ETHICS 1–10 (2020).
53 See also EMA, Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials, EMA/CHMP/BWP/534898/2008, September 2018.
54 For an early use of the expression, see Ariel Markowitz-Shulman et al., rapporteurs, Navigating the Manufacturing Process and Ensuring the Quality of Regenerative Medicine Therapies: PROCEEDINGS OF A WORKSHOP, National Academies of Sciences, Engineering, and Medicine, Forum on Regenerative Medicine, Washington (DC), October 26, 2017, 47 (2017).
Academic CAR-Ts represent a viable opportunity for producing and administering in-house CGTP/ATMPs to patients under the strict safety conditions required for clinical trials, at sustainable costs, and with promising results of efficacy, because of the simpler delivery processes. This regulatory path is not without precedent: ‘long before pharmaceutical companies took control of CAR-T, medical centers made these treatments. Cancer centers like the University of Pennsylvania, the National Cancer Institute, Memorial Sloan Kettering Cancer Center, Fred Hutchinson Cancer Center, Baylor University, and others figured out how to engineer CAR-T cells and ran the initial trials to test them. Drug companies were later involved mainly as a means to scale up production.’

It is worth noting that the same commercial CAR-Ts inherently maintain an experimental nature, starting from the fact that their development did not match the usual Phase I-II-III clinical trials pathway for assessing safety and efficacy. In fact, commercial CAR-Ts rely upon a common method of treatment for delivering an autologous therapy to a single patient based upon its unique biological material: as a consequence, usual replicability and comparability standards, as well as the ordinary progressive clinical stages, cannot be followed. In addition, peculiar issues surface even after the marketing approval. CAR-Ts are currently used as third-line therapeutic options, when patients are in critical conditions. Due to the ethical need to risk everything for saving a patient’s life, there have been cases where, even though the production batch did not meet the release specifications agreed upon between the medicine agencies and the pharmaceutical company to achieve a marketing authorization, the administering (and payment) of such products, known as Out-Of-Specification, has been permitted.

Furthermore, from a manufacturing perspective, according to available information, the manufacturing of commercial CAR-Ts relies upon the same closed, automated systems that are being used for delivering academic CAR-Ts. This supports the impression that, as it comes to these therapies, not only they flatly confirm the industrial biotech adagio that ‘the product is the process’, but what matters most are (third-party proprietary) methods of treatment able to comply with GMPs and the other standards established by applicable local rules, such as those relating to the need for hospitals and

55 David Mitchell, Saad Kenderian & S. Vincent Rajkumar, Letting Academic Medical Centers Make CAR-T Drugs Would Save Billions, STAT, November 20, 2019, https://www.statnews.com/2019/11/20/car-t-drugs-academic-medical-centers-save-billions/ (accessed Aug. 1, 2022). For a first-hand description of the process described here above, see Karlo Perica et al., Building a CAR Garage: Preparing for the Delivery of Commercial CAR T Cell Products at Memorial Sloan Kettering Cancer Center, 24 BIOL BLOOD MARROW TRANSPLANT 1135–1141 (2018).

56 Shirley Bartido, The Regulation of CAR-T Cells, 3 CELL GENE THER INSIGHTS 247 (2017).

57 This has been clearly stated by the FDA in a recent technical document: ‘Some CAR T cell attributes are intrinsically linked to attributes of the cellular starting material. Due to the inherent variability of the cellular starting material for autologous CAR T cells, using historical lots to assess comparability may not be adequate. We recommend that CAR T cell comparability be assessed by side-by-side testing using the same cellular starting material, when possible.’ (FDA, Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products—Draft Guidance for Industry, March 2022, 18, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products, accessed Aug. 1, 2022).

58 Alexey Bersenev & Sven Kili, Management of ‘Out Of Specification’ Commercial Autologous CAR-T Cell Products, 4 CELL GENE THER INSIGHTS 1051–1058 (2018). See also Elise Chong et al., Clinical Outcomes for Anti-CD19 CAR T Cell (CTL019) Products Not Meeting Commercial Release Specifications, 22 CYTOTHERAPY S29 (2020).
healthcare facilities to meet infrastructural requirements in order to administer CAR-Ts safely.\textsuperscript{59}

The in-house academic route is proving to be of particular interest to healthcare systems in many EU countries that have publicly owned (or privately owned but affiliated) infrastructures integrated with academic centers of excellence, in view of establishing national networks of CAR-Ts R&D activities. For instance, a project akin to this was launched in Italy, and in June 2021, public news appeared of three pediatric patients successfully treated through in-house experimental CAR-Ts manufactured and administered in a Roman clinical center of excellence, funded by a public grant to target a special type of leukemia (LLA-BCP) that proved refractory to conventional therapies.\textsuperscript{60}

In the presence of a therapeutically perfectly superimposable registered CAR-T, the use of an academic in-house CAR-T would not only be contrary to the principles of clinical trials’ legitimacy but would also violate the exclusive rights of third parties, both under a commercial and an intellectual property viewpoint. Still, the intrinsic radical individualization of autologous CAR-Ts determines wide margins of exclusive therapeutic applications for experimental drugs aimed at treating a single patient by means of her own engineered cells, without any overlapping with registered drugs as regards the required thorough verification of therapeutic equivalence between medicinal products.

Some difficulties to be expected in demonstrating the bio-similarity needed for supporting future developments of generic CAR-Ts have already been highlighted.\textsuperscript{61} Under a different perspective, other commentators remarked that ‘the many permutations by which to genetically construct a CAR allow multiple patents to be generated for the same disease, potentially avoiding patent infringement and advancing early market entry of competing products.’\textsuperscript{62} The multi-year-long (and multi-billion-worth) legal saga between Bristol Myers and Gilead subsidiaries, respectively, Juno and Kite Pharma, around the possible infringement by the latter of a patent referring to a chimeric receptor demonstrated how difficult it may be to prove an overlapping of critical components of CAR-T therapies even when it comes down to commercial versions aimed at being serialized.\textsuperscript{63}

\begin{itemize}
  \item \textsuperscript{59} Abigail Culshaw et al, \textit{Industrialization of an Academic Miltenyi Prodigy-Based CAR T Process}, 138 Blood 477–478 (2021).
  \item \textsuperscript{60} Italian Ministry of Health, \textit{Terapia delle leucemie con cellule CAR-T: primi tre bambini trattati con successo grazie alla produzione automatizzata sviluppata nell’ambito del Progetto CAR-T Italia}, press release no. 38/2021, June 8, 2021 (https://www.salute.gov.it/portale/news/p3_2_4_1_1.jsp?lingua=italiano&menu=salastampa&p=comunicatistampa&id=5804, accessed Aug. 1, 2022).
  \item \textsuperscript{61} ‘[…] The demonstration of biosimilarity for ATMPs is […] challenging because those products are often complex active substances, patient-specific (autologous), or require careful matching of donor and recipient (allogeneic). Moreover, only few validated biomarkers for establishing biosimilarity have been identified.’ (Enrique Seoane-Vazquez, Vaishali Shukla & Rosa Rodriguez-Monguio, \textit{Innovation and Competition in Advanced Therapy Medicinal Products}. 11 EMBO MOL MED 1–5 (2019)).
  \item \textsuperscript{62} Salvatore Fiorenza et al, \textit{supra} note 17, at 1710.
  \item \textsuperscript{63} Juno Therapeutics, Inc v. Kite Pharma, Inc., 20–1758 (Fed. Cir. 2021). For an introductory commentary to the last episode of this complex litigation, see Reed Slater, \textit{Bristol Myers Squibb Requests $1.2 Billion Patent Revival From Supreme Court}, \textit{Gene Online}, June 17, 2022, https://www.geneonline.com/bristol-myers-squibbs-requests-1-2-billion-patent-revival-from-supreme-court/ (accessed Aug. 1, 2022).
\end{itemize}
IV.B. In-House CAR-Ts and the HE

A further path for developing and administering non-commercial CAR-Ts is the HE. This is a special feature of the EU pharmaceutical regulation, currently not reflected in other legal systems, of great potential interest for the in-house national systems under development and also in view of bridging the academic developments envisioned here above.

The HE definition stems from article 3(7) of Directive 2001/83/EC (as amended by article 28 of Regulation 1394/2007/EC), which excludes the applicability of the general drug’s legislation to ‘any advanced therapy medicinal product [...] which is prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient.’

The HE allows for the individual preparation and administration of an ATMP (CAR-Ts included) under the responsibility of the doctor in charge of the patient. The exception clearly recalls the general model of so-called galenic or officinal formulations, ie preparing and compounding medicines on a tailor-made basis for matching in the best possible way the therapeutic needs of a given patient: all in all, an ancient and well-established version of personalized medicine.

In more detail, HE enables the manufacturing of ATMPs for treatment purposes outside of clinical trials, thereby exempting such products from both the application of clinical trial regulations and the EU centralized authorization proceedings for advanced therapies. HE was added to the two currently existing main pathways to make experimental drugs available to patients who are not enrolled in clinical trials, ie, respectively, named patient use and compassionate use. In doing so, however, HE expands the viability of autonomous pharmaceutical point-of-care-based productions of advanced therapies based upon decentralized manufacturing on a truly different scale, without lowering the quality and safety standards required along the path of clinical trials and in the commercial phase of products authorized for sale. This is because the current EU applicable regulation, while introducing the HE within the ATMP regulatory framework, clearly states that the manufacturing of products made through such exemption ‘shall be authorised by the competent authority of the Member State. Member States shall ensure that national traceability and pharmacovigilance requirements as well as the specific quality standards referred to in this paragraph are equivalent to those provided for at Community level in respect of advanced therapy medicinal products for which authorisation is required pursuant to Regulation (EC) No 726/2004’ (cf. article 3(7) of amended Directive 2001/83/EC).

As a consequence, responsible subjects of in-house HE-based operations refer to national medicines agencies or other competent authorities (eg specialized offices at

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64 The EU legislation, at article 3(3) of Directive 2001/83/EC, refers to ‘Any medicinal product which is prepared in a pharmacy in accordance with the prescriptions of a pharmacopoeia and is intended to be supplied directly to the patients served by the pharmacy in question (commonly known as the officinal formula)’. For a reference to a similar exception within the US regulatory system, cf. section 503A of the Federal Food, Drug, and Cosmetic Act, about pharmaceutical compounding.

65 Delphi Coppens et al., Advanced Therapy Medicinal Product Manufacturing Under the Hospital Exemption and Other Exemption Pathways in Seven European Union Countries, 22 CYTOThERAPY 593 (2020).
ministries of health) for every issue related to GMPs compliance, technical equipment and infrastructural requirements, as well as for pharmacovigilance activities, thus ‘mimicking’ the safety and efficacy standards for commercial products.

The now applicable EU rule refers to national regulations and related involvement of locally competent medicine agencies for authorizing the products with a State-wide validity. According to recent surveys, at least nine European countries effectively enacted the HE principle at a national level: Belgium, Finland, France, Germany, Italy, the Netherlands, Spain, Poland, and the UK, with ca. 70 public manufacturing facilities currently developing HE-based ATMPs.

Due to the referral to national sub-systems of rules, a relevant implication of the current HE model has been the fragmentation of operational regulations. Moreover, in the pharmaceutical context of highly technical and administratively secluded rule making, the need to develop national norms and enforcement routes for providing substance to complex concepts, such as ‘non-routine basis’, evidently did not help in establishing a clear and common framework for HEs.

Unsurprisingly, heterogeneity of HE implementation rules and interpretation standards has already been pointed out as a serious limiting factor in the affirmation of transnational cooperation in HE-ATMPs. The national characteristics of the HE implementation process is also quite often subjected to the need to align the new regulation with pre-existing provisions. This has led to different orientations with respect to the same purposes of the exception to be considered more relevant, and oscillations have been reported between rules aimed at responding primarily to unmet health needs or providing treatments with a sustainable benefit/risk ratio.

Even with these predictable challenges, the mandatory reference for HE-based CAR-Ts to specific ATMPs GMPs valid on an EU-wide basis helped to define a technical level playing field for this type of production. As for the possibility that important notions may vary according to different legal systems, it appears safe to consider that this was a foreseeable consequence of the original EU-HE rule, which allow each Member State, at least during an initial ‘launch phase’ of the new regulation, to fine-tune the exact number of patients to be treated by means of an HE-based ATMP with its specific population and related therapeutic needs. The fact that the fundamental effect of the EU-HE rule has been to transfer to a national level the product’s authorization, further supports the interpretation provided here above. In any case, due to the very personal nature of CAR-Ts developed so far, at least for this specific type of ATMP, the issue of non-routinary manufacturing does not seem to play any role, as every autologous CAR-T treatment is necessarily unique.

66 Delphi Coppens et al., Regulating Advanced Therapy Medicinal Products Through the Hospital Exemption: An Analysis of Regulatory Approaches in Nine EU Countries, 15 Regen Med 2015–2028 (2020); for an HE regulatory survey and critical comments from the pharmaceutical industry side, see Allison Hills et al., An Assessment of the Hospital Exemption Landscape Across European Member States: Regulatory Frameworks, Use and Impact, 22 Cytotherapy 772–779 (2020). For a case-study of HE practicability among the EU Member States that enacted national rules (namely, Italy), see Luca Arnaudo, CAR-T, modelli inhouse per retinazionaliedeccezioneospedaliera: prospettive in Italia, 113 Recenti Prog Med 1–6 (2022).

67 Esteve Trías et al., The Hospital Exception Pathway for the Approval of Advanced Therapy Medicinal Products: An Underused Opportunity? The Case of the CAR-T ARI-0001, 57 Bone Marrow Transpl 157 (2022).

68 Delphi Coppens et al., supra note 66, at 2022.
The anticipated reform of the EU drug regulation will constitute an important opportunity to consolidate both experiences and knowledge accumulated up to now in the field of HE. An example could be the adoption at a centralized level of some operational criteria that proved to work properly at a national level.

**IV.B.1. HE practical applications to CAR-Ts**

Until recently, none of the ATMPs produced so far under an HE according to EU regulation was a CAR-T. In February 2021, however, the scenario completely changed with news from Spain of the first authorization of an in-house HE-based CAR-T.

ARI-0001 is the reference name of ‘the first CAT to have been developed from bench to bedside in the European Union – more specifically in Barcelona, Spain – and the first to receive the authorization of a governmental drug agency outside the centralized marketing authorization pathway (ie under non-industrial conditions but similar quality, safety, and efficacy standards) foreseen by the European ATMP Regulation’.

The triumphal tone of the quote is well deserved, since ARI-0001, that has been approved for a special type of leukemia in a population (young adults up to age 25) not targeted by any available commercial therapy, represents a fundamental testbed for the viability of further CAR-Ts development under the EU-HE-ATMPs regime.

Funded by a joint effort of public authorities and civil society, with donations made by thousands of individuals, associations, and companies, ARI-0001 moved successfully from a phase of academic experimental drugs to regulatory national approval as an HE-based therapy. According to the researchers involved in its development under the HE-ATMPs pathway, ARI-0001 is currently reimbursed by the Spanish national healthcare system at a price that is one-third of the commercial CAR-Ts already marketed in Spain. In terms of further developing the availability of such therapy at affordable costs, sub-licensing of relevant intellectual property rights to projects of other Member states/national health systems with similar purposes could be considered.

**V. CONCLUSIONS**

CAR-Ts are set to profoundly change the therapeutic strategies for an increasing number of severe diseases, even beyond the current focus on blood tumors. The expectations surrounding these innovative therapies are not surprising: at the same time, concerns recur from a third-party payer (either public or private) viewpoint about their economic sustainability at the current prices, considering that applications will most surely enlarge and overall costs consequently expand.

Framed in this context, current projects related to the development of in-house CAR-Ts are of great interest, especially those referring to academic productions all

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69 Esteve Trias et al., *supra* note 67, at 156. See also AEMPS, press release MUH 4/2021, February 10, 2021.
70 Maria Castella et al., *Point-Of-Care CAR T-Cell Production (ARI-0001) Using a Closed Semi-automatic Bioreactor: Experience from an Academic Phase I Clinical Trial*, 20 FRONT IMMUNOL 1–13 (2020).
71 Manel Juan et al., *Is Hospital Exemption an Alternative or a Bridge to European Medicines Agency for Developing Academic Chimeric Antigen Receptor T-Cell in Europe? Our Experience with ARI-0001*, 32 HUM GENE THER 19–20 (2021).
72 Esteve Trias et al., *supra* note 67, at 159.
around the world, and so far only in Europe those relying upon the HE discussed in this article. In a broader perspective, the decentralization of production and management activities in strictly controlled safety conditions could be the most effective solution to allow access to advanced therapies (inside or even outside the richest healthcare systems), in line with recurring calls for health equity that the Covid-19 pandemic has made even more pressing.73

The argument for decentralized production and administration is not necessarily in contrast with further developments of commercial therapies. In fact, on one hand, the in-house point-of-care models of national hospital networks could find their operative area of choice in the production of autologous CAR-Ts, focusing first and foremost on niche unmet medical needs. By leveraging the advantages of decentralization for guaranteeing ‘fresh’ products, this would enhance in the highest and most efficient way the profile of personalized medicine of these therapies at affordable costs, also exerting a virtuous competitive pressure on the pharmaceutical industry to maintain reasonable prices for its advanced therapies. On the other hand, the vibrant research paths toward allogeneic ‘off-the-shelf’ CAR-Ts open bright perspectives for standardizable products that are more compatible with broader business strategies (and, again, with more sustainable costs to be reflected by final prices).

To achieve such a complementary division of activities, it is critical to reach an alignment in the different legal systems with regards to operating conditions, from R&D (testing, GMPs compliance) to distribution conditions (eg labeling). Provided the need to further enhance the knowledgeability and stability of existing national regulations and procedures, the HE established by the current EU ATMP regulation and expected to be confirmed within the incoming reform of the EU pharmaceutical legislative framework could be a viable common ground on which to meet other legal systems, starting with the USA.

Such a legal transplant appears to be easier than a radical revision, as has been proposed by some commentators, of the US ‘351’ drug paradigm for CAR-Ts in view of scaling them back to the US ‘361’ non-drug status. From a regulatory perspective, the author of this article agrees with the idea that CAR-Ts share relevant similarities with methods of medical treatment. Having said that, it is frankly difficult to imagine a plain return to a non-drug assessment and simplified regulatory management in the presence of various CAR-Ts already registered as medicinal products and marketed as such. Moreover, the stringent pharmacovigilance rules established for medicines better support a prolonged monitoring of the uses and effects of CAR-Ts, a much-needed precaution due to the substantial side-effects currently attached to them.

On a broader perspective, in order to properly cope with advanced therapies (such as CAR-Ts) where the boundaries between methods of treatment and extremely personalized gene and cell-based medicines are difficult to firmly outline, it would be useful to seriously consider the need to effectively establish a third product category, halfway between drugs and treatments, possibly by embracing a flexible regulation combined with ‘an adaptive societal governance’74 able to better manage the conceptual uncer-

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73 Muin Khoury et al., Health Equity in the Implementation of Genomics and Precision Medicine: A Public Health Imperative, 24 GENET. MED. 1–10 (2022).
74 Miranda Mourby et al., supra note 37, at 27.
tainties attached to new biomodifying technologies. This might also allow to better fine-tune regulations related to intellectual property, exclusivity rights, and licensing policies, according to relevant product characteristics.

In the new and emerging field of CAR-Ts, we are moving in frontier territories. The purpose of this exploration is to help frame the best possible pathways for delivering innovative gene and cell-based medicines and therapies. Decentralized in-house models, such as the academic and HE discussed in this article, help guarantee sustainable and equitable access to existing treatments and support the effective development of new ones.