CHAPTER 28

Commercialising CAR-T Therapies: The Evolution of a Revolution

Emanuele Ostuni, Bernd Eschgfaeller, William Chou, Irene Aldecoa Bilbao, Kristen Harrington-Smith, Etienne Jousseaume, Marieke Jansen, Simona Paratore, Matthew Robson, Jie Zhang, Fiona Phillips, Karin Blumer
Novartis Oncology Cell and Gene Therapy Europe, Basel, Switzerland

INTRODUCTION

In August 2017, the FDA issued a press release in which it announced a '*historic action […] making the first gene therapy available in the United States, ushering in a new approach to the treatment of cancer*' (Food and Drug Administration, 2017). The treatment to which this announcement referred was the first ever approved CAR-T ('chimeric antigen receptor T cell') therapy, a novel approach to genetically modify a patient's own immune cells to enable them to effectively detect and destroy cancer cells. Following FDA approval, Kymriah, pioneered by a collaboration between the University of Pennsylvania and Novartis, became the first CAR-T therapy to be approved in Switzerland, Japan, Canada and Australia and the first CAR-T therapy to be approved for two distinct indications in the European Union.

CAR-T therapy is not a traditional pharmaceutical product, and in fact, it is a new type of product altogether. Traditional pharmaceuticals are either small molecules (i.e., substances that are produced in chemical manufacturing units and are mostly administered as pills, injections or ointments/creams) or biopharmaceuticals (therapeutic proteins that are produced in bioreactors with the help of living cells and usually administered as injections). More recently, cell-based products have reached the market; these aim to treat disease by restoring or altering certain sets of cells or using cells to carry a therapy through the body. Gene therapies, which aim to treat diseases by replacing, inactivating or introducing genes into cells – either in vivo or ex vivo – are now on the horizon.

CAR-T is radically different from traditional small molecule and biopharmaceutical products, and it combines elements of cell-based medicines and gene therapy and qualifies as an immunotherapy. The 2017-approved medicine is an autologous CAR-T, a medicine that is based on a patient's own T lymphocytes. One of the first steps involves sophisticated cell filtration ('leukapheresis') to harvest a patient's T cells – a subset of white blood cells that play a central role in the immune system. In a complex process, these cells undergo an in vitro gene modification where a therapeutic gene construct is

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inserted. This encodes for an anti-CD19 receptor that is expressed on the modified T cell surface (the 'CAR', chimeric antigen receptor). This receptor enables the modified T cells (now the 'CAR'-T or CAR-T cells) to specifically detect and destroy cells that are positive for the cell surface protein CD19 – which is expressed in some cancers such as some leukaemias or lymphomas. Other chapters in this book provide a thorough description of the science and cancer applications of current CAR-T therapy and the potential for future development.

The final product is a genetically modified living cell suspension, which is administered as an intravenous infusion. With a single treatment, the patient's body can harness the power of its immune system and fight the cancer.

The FDA's press release marked the starting point of a unique commercialisation journey for Novartis and the stakeholders in the US healthcare system. The chosen wording of the press release was testimony to the transformational impact the commercialisation of CAR-T therapies means for many stakeholders, including regulatory authorities.

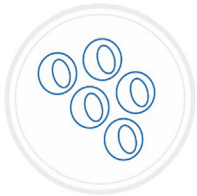
This chapter aims to share some of the key learning so far, at a time when commercialisation in key regions is ongoing. In the first section, we will share the history of Novartis' CAR-T journey. The second section will look into the clinical development of the first commercial CAR-T therapy before a third section, which will share key features of the new business model. Sections four and five will give an overview of the value propositions and pricing considerations for this unique 'living' medicine and share an industry perspective on responsibility in commercialising breakthrough innovation. The final section will highlight key topics that require attention to ensure the future of CAR-T and other cell and gene therapies (Fig. 28.1).

THE NOVARTIS JOURNEY TO CAR-T CELL THERAPIES

Over the last decades, Novartis has built a strong legacy in the area of haematology. A prominent example was imatinib, which received FDA and European Medicines Agency (EMA) approval in 2001. At that time, this compound (marketed as Gleevec in the United States and as Glivec ex-US) was one of the first, truly targeted cancer therapies brought to market with lifesaving effects in a rare form of blood cancer – chronic myeloid leukaemia (CML).

The imatinib journey provides important context to understand the internal and external environment in which CAR-T therapy entered the research and development space. There are many similarities between the imatinib and CAR-T therapy discovery journey, so when Novartis invested in CAR-T therapies, there was a basic understanding of the scale of challenges that could arise.

The imatinib discovery took place before Novartis was formed in a merger between the two Basel-based pharmaceutical companies Sandoz and Ciba-Geigy. Towards the



Cell therapy aims to treat diseases by restoring or altering certain sets of cells or by using cells to carry a therapy through the body[5]. With cell therapy, cells are cultivated or modified outside the body before being injected into the patient. The cells may originate from the patient (autologous cells) or a donor (allogeneic cells)[6].

Gene therapy aims to treat diseases by replacing, inactivating or introducing genes into cells—either inside the body (in vivo) or outside of the body (ex vivo)[6].

Some therapies are considered both cell and gene therapies. CAR-T is a combination of cell and gene therapy as they alter genes of specific cells (T-cells) which are re-inserted in the body. CAR-T therapies modify the immune system, thus they can also be considered as immunotherapies.

Figure 28.1 The difference between cell therapy and gene therapy.

end of the last century, only a few pharmaceutical companies were investing into tyrosine kinase inhibitor research and development (Pray, 2008). In 1992, Ciba-Geigy and Oregon Health and Science University entered into a critical industry–academic collaboration, which would see the testing and marketing of imatinib as a commercial product. In 1996, the imatinib journey hit its first bump in the road as Ciba-Geigy merged with Sandoz to become Novartis. There was some uncertainty about further developing the product as significant doubts about the likelihood of approval and the commercial viability of a drug for such a small patient population were discussed. Convinced by the lifesaving potential of the drug, the newly formed Novartis took a first original leap into reimagining medicine and, in 1998, imatinib entered the first phase of clinical trials. All patients achieved complete remission (Pray, 2008; Grindlinger, 2009), leading to accelerated FDA approval of imatinib in May 2001. The impressive potential of imatinib caught media attention, and imatinib appeared on the front cover of Time magazine, hailed as the magic bullet in the war against cancer (Grindlinger, 2009; Park MDLaA, 2001). The public visibility of this drug was something oncology had rarely seen before, and with the lifesaving nature of the medicine came an immense moral and societal responsibility.

Today many oncologists consider CML no longer a fatal cancer but a chronic disease (Grindlinger, 2009). The discovery, development and successful commercialisation of imatinib helped establishing a new group of cancer drugs: targeted therapies (National Cancer Institute, 2018a,b). The discovery of targeted therapies has gone on to transform the study and treatment of cancer and has fostered the precision medicine approach:

treatment tailored to the unique genetic changes in an individual's cancer cells (National Cancer Institute, 2017, 2018a).

In 2012, strong from the experience of taking a drug from a collaborative discovery to full-scale commercialisation, and transforming research and treatment approaches on the way, Novartis entered into a new partnership.

In 2011, a similarly transformative science began to emerge: individualised CAR-T immunotherapy showed breakthrough results in the treatment of chronic lymphocytic leukaemia in several patients (Penn Medicine News, 2012). The power of this discovery is demonstrated through the story of a 7-year-old child with acute lymphoblastic leukaemia (ALL).

On 17 April 2012, Emily Whitehead became the first paediatric patient to be treated with a CAR-T cell therapy (Children's Hospital of Ph, 2019). Three weeks after the successful CAR-T cell infusion, a bone marrow test showed that the therapy had resulted in a complete remission, which is still the case at the time of writing this chapter (Children's Hospital of Philadelphia, 2019).

Emily's story made headlines across the globe and brought the spotlight to cancer immunotherapy (Grady, 2012). Leading scientists in the Novartis Institutes for Biomedical Research became aware of this story, and in August 2012, Novartis entered into a specific collaboration with the University of Pennsylvania. This move made Novartis the first pharmaceutical company to invest in this cutting edge research (Penn Medicine News, 2012). Novartis acquired an exclusive worldwide licence for the CAR-based therapies that were undergoing trial, as well as any future therapies developed through the collaboration. Together, the University of Pennsylvania and Novartis built the first-of-its-kind Center for Advanced Cellular Therapeutics, opened in 2016, which has since developed into an epicentre for research and early development of personalised cell therapies (Penn Medicine News, 2012).

In December 2012, only 3 months after the initial collaboration with the University of Pennsylvania, Novartis acquired an FDA-approved manufacturing facility in Morris Plains, New Jersey, from the biopharmaceutical company Dendreon. The facility was dedicated to supporting the clinical and commercial production of personalised cell therapies from the Center for Advanced Cellular Therapeutics (Palmer, 20122).

Novartis has since continued their journey of collaboration across the globe. To increase the production of CAR-T therapies, Novartis entered into collaboration with the Fraunhofer Institute for Cell Therapy in Germany in 2015 (Fraunhofer, 2015), the Foundation for Biomedical Research and Innovation in Japan in 2017, the Cellular Biomedicine Group in China in 2018 (CBMG, 2018) and acquired CELL*for*CURE in France in 2018 (Novartis.com, 2018). Also, in 2018, the company announced the establishment of a new CAR-T manufacturing site in Stein/Switzerland.

Novartis' spirit of collaborative innovation has also led to agreements that promise further development of the CAR-T therapy portfolio; in 2018, they entered into collaboration with BioCurate Pty Ltd. in Australia to accelerate early stage drug discovery, and in

2019, the company invested in US-based Poseida Therapeutics to trial a new CAR-T therapy for multiple myeloma. These clinical stage collaborations add to the growing list of preclinical collaborations in several areas including novel gene-editing approaches.

GLOBAL CLINICAL DEVELOPMENT AND REGULATORY APPROVAL

It was clear that CAR-T cells had the potential to transform outcomes for patients suffering from ALL, and this was echoed by the FDA who designated Novartis CAR-T therapy a Breakthrough Therapy in July 2014 for relapsed and refractory paediatric and young adult ALL.

In April 2015, the first paediatric participant was enrolled in a 7-year phase II clinical trial that assessed the efficacy and safety of CTL019 in children and young adults with relapsed or refractory (r/r) ALL (ELIANA) (U.S. National Library of Medicine, 2018). The ELIANA study treated 75 patients in 25 study centres across 11 countries, making it the first ever global CAR-T clinical trial (U.S. National Library of Medicine, 2018).

The initiation of this study was closely followed by an 8-year study of CTL019 in adults with r/r diffuse large b-cell lymphoma (DLBCL) (JULIET) in May 2015. This study treated 101 patients in 27 study centres across 10 countries, making this study the first global CAR-T trial in adult DLBCL patients (U.S. National Library of Medicine, 2019).

Both trials were single arm due to the rarity of the diseases and the lack of satisfactory treatment available at the time. Generally, good clinical practice considers it unethical to conduct a randomised, controlled trial in a situation where there is no comparator option that provides a durable benefit or is of curative potential for these patients. In such a setting, strong clinical results are demanded by regulatory authorities to grant approval (DeAngelo et al., 2007; Jeha et al., 2006; Ottmann et al., 2002; Topp et al., 2014).

The initial results from the ELIANA study were impressive, with an 82% overall remission rate which was sustained at 6 months (Novartis, 2017a). In recognition of CAR-T therapy's potential to address an unmet medical need, the EMA designated CAR-T therapy a Priority Medicine for r/r paediatric ALL in January 2016.

During this time, high-cost cell and gene therapies were being heavily scrutinised in the media spotlight. In 2012, UniQure biopharma B.V's gene therapy Glybera was the first ever gene therapy approved in Europe (European Medicines Agency, 2017; European Biotechnology, 2017). In 2017, following many challenges around the medicine's value and pricing, it was out phased from the European market and it never received regulatory approval in the United States. (European Medicines Agency, 2017) It was in this context that the US FDA-approved Novartis' CAR-T therapy for patients under 25 years of age with r/r ALL in August 2017. Novartis offered here an outcome-based reimbursement agreement for this indication of CAR-T (Novartis, 2017b). Payment was due only if the patient responded to the treatment by the end of the first month postinfusion (Novartis, 2017b). This was an important development in moving

traditional reimbursement models forward into something more suitable for high-value, one-treatment, cell and gene therapies.

In April 2017, the FDA designated the same CAR-T therapy with breakthrough therapy status for relapsed and refractory DLBCL (Novartis, 2017c). Following the first approval by the FDA, Novartis applied for the medicine's approval in the European Union, Australia, Switzerland, Canada and Japan between October 2017 and April 2018. Novartis triggered these applications because the lifesaving potential of this treatment necessitates the broadest possible patient access around the globe. As this chapter is authored, Novartis continues to seek regulatory approval in other markets and regions.

In March 2018, the FDA approved Kymriah in DLBCL, 5 months before the European Commission's approval for both indications in August 2018. Three more approvals happened in 2018 with Health Canada in September, Swiss Medic in October and the Therapeutic Goods Administration in Australia in December – each of them valid for both indications. In 2019, the therapy also became the first ever approved CAR-T therapy in Asia after approval by Japan's Ministry of Health, Labour and Welfare.

FROM PROCESS TO PRODUCT – CREATING A NEW BUSINESS MODEL

Regulatory approval is the peak of an innovative medicine's research and development journey. It is the endpoint of a long and risky process, which starts with the sound understanding of the causal disease mechanisms, followed by the identification of a 'druggable' target, discovery of a drug that matches the target and successful preclinical and clinical studies, and leads eventually to regulatory approval of this new medicine. In the public notion, an FDA or EMA approval is often misinterpreted as the end of the innovation story, followed 'only' by the marketing and commercialisation of the new product, i.e., the phase where the pharmaceutical industry is harvesting the fruits of research and development and recouping the upfront investment.

Innovation happening in the commercial space is often underestimated – but in the case of CAR-T therapies, the field is so young that the manifold innovation needed to successfully bring this therapy to market is not even yet fully understood. This section aims to contribute to close this gap by sharing the Novartis commercial experience covering United States, the European Union's Member States, Switzerland, Norway and Israel. Novartis is in middle of this undertaking while this chapter is being written. Commercial launch in Canada, Australia and Japan started in 2019, when this chapter was completed, and will not be described here.

The following section will focus on two central areas of commercial innovation in the space of CAR-T:

(A) The transformation of the customer/business model: from B2B (business to business) to B2P (business to provider/patient)
(B) Collaborating with hospitals – from medicine provider to treatment partner

These focus areas are all deeply linked to the unconventional way in which CAR-T therapies are manufactured and delivered. The process is fundamentally different from the traditional innovative pharmaceutical business model, which is organised linearly from the manufacturer/developer to the patient by way of physicians.

Transforming the Customer/Business Model: From B2B to B2P

The manufacturing and distribution of autologous CAR-T cell therapies has a profound impact on the industry's relation to healthcare providers and patients. Traditionally, the industry delivers therapies to physicians and patients indirectly, through other businesses. In autologous CAR-T, this business-to-business (B2B) model is replaced by a direct delivery from the manufacturer to the patient's point of care. We will describe this radically new model as a *business-to-provider/patient* or *B2P* model. Although we will describe the Novartis approach to the commercialisation of CAR-T therapies, we believe the key elements presented here could be shared by multiple manufacturers.

In the conventional manufacturing and distribution model, a medicine (e.g., small molecule or biopharmaceutical), which successfully passed the scientific discovery process, undergoes technical development during the clinical development phase. Small units are produced to sustain supply to clinical trial centres while formulations and production are prepared for mass production. Multiple sources deliver the manufacturing starting material, either in form of traditional chemical compounds in the case of small molecules or in the form of standardised living cell lines and cell nutrition media in the case of biopharmaceuticals.

After regulatory approval, manufacturing capacity is adapted to the growing demand and commercial packaging is introduced in the process. The final, packed medicine is handed over to the distribution chain. This step is usually handled by third parties, and logistic companies work together with wholesalers to secure delivery to pharmacies, hospitals or other entities. Ultimately, the patient receives the medication either in a hospital or – after a physician's prescription – in an outpatient setting as pickup from a retail pharmacy.

Calculated overproduction can help to mitigate a risk of manufacturing or transport chain disruption as the final product can be stockpiled at multiple points in the supply chain for periods of time, typically longer than 1 year. Quality controls are conducted at different points in the chain, most importantly before product release in the manufacturing site and as batch controls after transport/import.

In this traditional model, the manufacturer has no direct contact with the customer and both 'the physician' and 'the patient' are usually unknown individuals; therapy is not truly personalised for each individual patient.

As Fig. 28.2 outlines, the manufacturing and distribution model in the case of autologous CAR-T cells is intrinsically different from any traditional small molecule or biopharmaceutical medicine. It is a circular process, whereby the individual patient marks both, the beginning and the end of each single CAR-T batch.

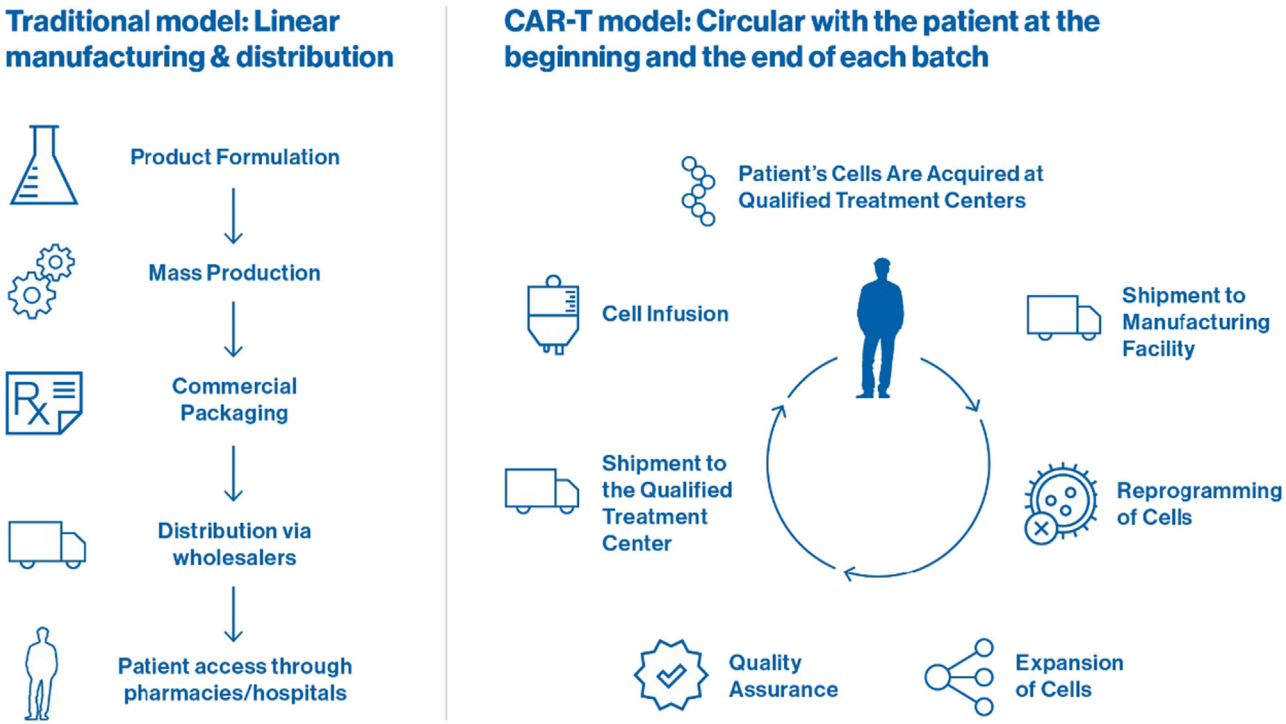


Figure 28.2 Simplified comparison of the traditional, linear medicine manufacturing and distribution model with the circular chimeric antigen receptor T cell (CAR-T) model.

Figure 28.3 Arrival of leukapheresis material at the manufacturing plant. On the floor left to the operator is the transport Dewar; cell material is inside the cassette held by the operator.

At the beginning of this truly personalised manufacturing process stands the identification of a patient eligible for treatment by a physician in a qualified treatment centre. Once treatment eligibility is confirmed, the physician contacts the CAR-T manufacturer to place an order. In the case of Novartis, this happens through the placement of a product request by the physician on a web-based order platform. This IT interface is directly linked to Novartis and the manufacturing site.

After order confirmation, the patient's cryopreserved aphaeresis material is picked up and prepared for shipment. This process has been chosen by Novartis to overcome some of the limitations in using fresh cell material that must reach the manufacturing site as soon as possible, usually within 48 h. Special transport dry shippers ('Dewar[s]' see Fig. 28.3) allow cryopreservation for up to 1 week and enable safer shipping, as interruptions of the transport chain have no negative impact on the cell material. Outside of the transport chain, cryotanks can be used for long-term storage of the cell material.

To ensure secure maintenance of the chain of identity, the bag with the cell material must be equipped with unique ID labels that contain secure patient identifiers. Technical devices securely control the temperature, and thanks to a GPS tracker, the Dewar's geoposition can be tracked in real time.

At the manufacturing site, the cells undergo the genetic reprogramming and expansion process. A viral vector is used to insert the CAR-coding gene into the nuclear DNA of the T cells. Every batch of modified cells undergoes a rigorous quality control before a second cryopreservation and is shipped back to the patient's treating centre. On arrival, cells are thawed, and a single intravenous infusion of the CAR-T cells initiates the factual treatment. If successful, the modified cells target and destroy the patient's cancer

cells. CAR-T cells work as a living medicine. They expand and persist inside the patient's body and can deliver a deep and durable response after a one-time administration only.[1]

The circular nature of the process has manifold, profound implications, not all of which can be discussed in full detail here as this would exceed the scope of a chapter.

The most meaningful implication is the central role of the individual patient. The patient is literally at the beginning of each manufacturing cycle and at the end of the final delivery process as the recipient of the therapy. Patients entrust their own cells to a process that may be a last hope for survival. Also, the role of the hospital changes fundamentally. It is no longer only a recipient of a product but also through the aphaeresis unit a provider of material that (after processing at the manufacturer's facilities) will become starting material for manufacturing – the patient's T cells. The identity of these cells must be fully protected throughout the whole process. If ever the cells of two patients were to be wrongfully exchanged, the lives of two persons would be at risk. To mitigate this risk, Novartis had to develop and integrate a thorough mechanism to protect the chain of identity throughout the 'vein-to-vein' cell journey, including in the IT system, during packaging and shipping, within the manufacturing facility and again, back to the treatment centre. This required a novel web-based platform, the Novartis CellChain and supporting services that have been unique in the company. Notably, regulatory authorities and Novartis jointly agreed that a patient's full name and date of birth constitute unique identifiers for a secure chain of identity, and various checks and controls need to be embedded along the 'vein-to-vein' cell journey. In many legislations, e.g., throughout the European Union which just adopted a very stringent data privacy legislation in 2018 (European Commission, 2018), personal health data are subject to highest protection standards which also put strict regulations onto cross-border data exchange. This added to the complexity of developing a functional and fully reliable chain of identity system.

Quite understandably, for physicians and patients, the ordering of a CAR-T treatment cannot be compared with any normal product order. It is not only a bag of frozen cells which is being shipped; the status of this order impacts a patient's chance of survival. At a time where people have become used to tracking conventional product orders – e.g., placed via Amazon – almost in real time, highest quality customer service is almost mandatory in the autologous CAR-T business model. Novartis has put this at the core of its operations.

A dedicated, multilingual service team is operating in multiple geographies within the within the Novartis customer service center. This team comprises experts with the necessary technical and medical expertise to answer potential questions of treating

[1] The ELIANA trial showed an 83% overall remission rate (ORR) in paediatric and young adult pALL at 12 months, which was sustained at 24 months (82% ORR).18. Novartis. 2017. The ELIANA Clinical Trial Fact Sheet. Available from: https://novartis.gcs-web.com/static-files/110bee95-5916-483f-a0c9-20128105005f. The JULIET study showed a 52% overall remission rate in adult DLBCL at 14 months which was sustained at 19 months (54% ORR)23. Novartis. 2019. JULIET Clinical Trial Fact Sheet.

physicians and other healthcare professionals throughout the process. The objective of this team is to provide a central service and information hub to treatment centres. The hub is a readily accessible support system that makes the whole product ordering, processing and product receipt process as easy to navigate as possible. The service team's responsiveness aims to enable a high percentage of first contact resolutions and to give clarity and visibility to the different steps of the cell's journey. We believe this is a key attribute of the business model for autologous cell therapies.

Ultimately, the combination of the CellChain platform, local customer facing functions and the service team allows physicians to plan the treatment for each patient thoroughly – even before a product request is placed – and to react to all situations appropriately.

On a healthcare systems level, the consequences of the circular, B2P model may have quite profound long-term implications. For autologous CAR-T therapies, traditional wholesalers may no longer be a part of the supply chain. With CellChain, a sophisticated, secure ordering and tracking platform has been established, which allows healthcare professionals to place orders directly and track the status of their order in real time. As more and more cell and gene therapies are coming to market, a universal solution for such order systems might be required in the medium- to long- term. As digitalisation increases throughout all levels of patient and hospital management, such novel platforms have transformative potential way beyond CAR-T therapies.

Collaboration With Hospitals – From Medicine Providers to Treatment Providers

As CAR-T therapies reach the market, they cannot be used by any hospital. Treating patients with CAR-T cells requires unique expertise, specialised equipment and facilities; thus, training is required, and a centre qualification process by the manufacturer of the therapy has been set up as regulatory requirement by regulatory agencies globally. During this qualification process, a hospital becomes a qualified CAR-T treatment centre. Such centre qualification for marketed therapies is a rather unique process for the pharmaceutical industry. A high level of expertise plus a broad range of advanced technical equipment must exist before a hospital can become a qualified treatment centre for commercial CAR-T therapies (an overview is presented in Fig. 28.4). Eligibility criteria for treatment centres, where the CAR-T cells are infused, include, amongst others

- High expertise with stem cell transplants in the disease area,
- Presence of an expert physician in treated disease areas with an established referral network,
- ICU capabilities to manage potential adverse events,
- Patient support infrastructure,
- Availability of support services for patients and caregivers, etc.

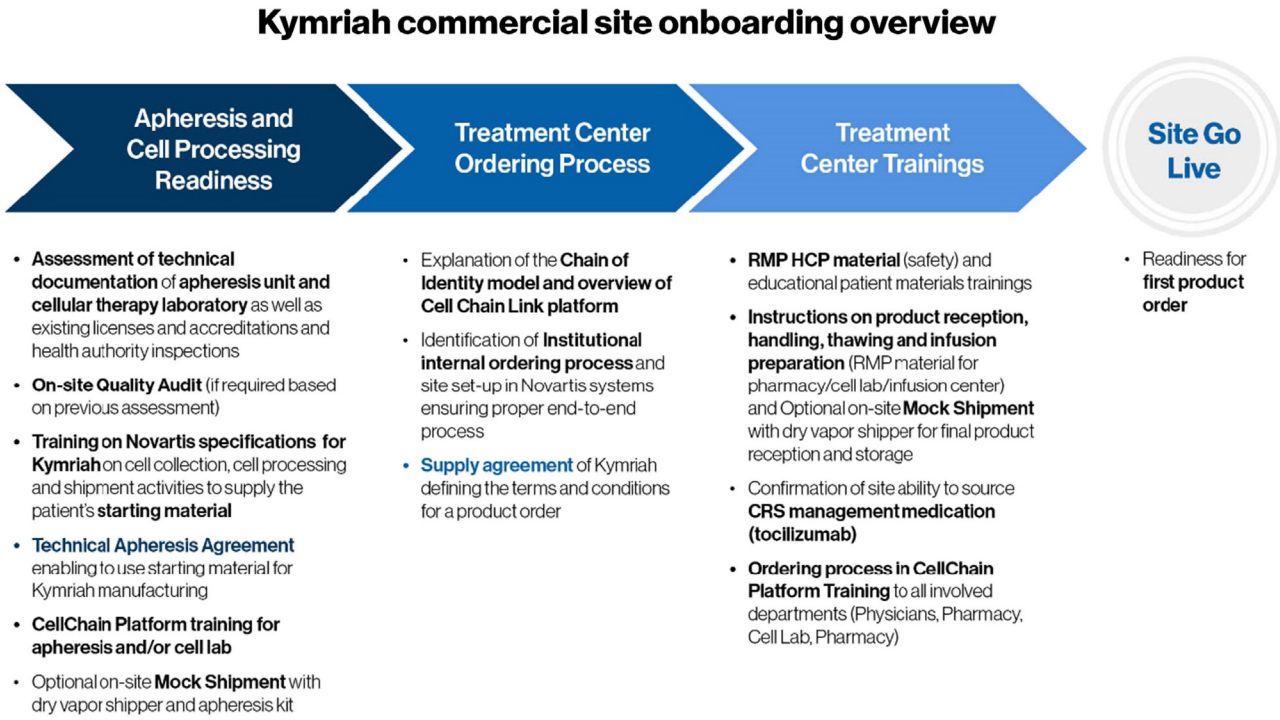


Figure 28.4 Overview of the Novartis onboarding process for commercial CAR-T treatment centres.

Regarding an aphaeresis unit and cell therapy laboratory, Novartis centre qualification criteria stipulate that facilities have an appropriate and up-to-date competent health authority's accreditation for cell collection, cell processing and cryopreservation, a solid Quality Management System, adequate equipment such as a controlled rate freezer and cryostorage capacity and patient materials labelling capabilities to ensure the integrity of the chain of identity.

Novartis' CAR-T therapy is supplied to treatment centres under a controlled distribution programme to mitigate the safety risks associated with the therapy. Healthcare professionals involved in the treatment of a patient have completed a tailored, specialised educational programme. To manage CRS (cytokine release syndrome, a potential side effect of the therapy), these centres also must have on-site, immediate access to tocilizumab, which is a key treatment for one of the more serious side effects of CAR-T therapies.

Novartis developed a specialised centre qualification process to meet all the necessary steps and requirements. Qualification is granted once all criteria are met. Examples of qualification criteria include

- Confirmed completion of a healthcare professional educational programme with focus on risks of key adverse events, including CRS,
- Full availability ensured of on-site, immediate access to tocilizumab as CRS management medication before treating patients,
- Confirmed completion of the healthcare professional training on patient information pack and patient consent information,
- Technical survey of the aphaeresis institution and cell lab in accordance with the EU Good Manufacturing Practice Guidelines on Good Manufacturing Practice specific to Advanced Therapy Medicinal Products,
- Technical quality assessment of aphaeresis centre's cell-processing laboratory and aphaeresis collection facility with a quality audit, if deemed required,
- Instructions on final product reception and storage in the cell-processing facility, instructions for coordination of product and patient preparation for infusion and for infusion including handling prior to infusion, thawing procedure, administration and monitoring after infusion,
- Training on ordering process including chain of identity education.

Although the medical community is developing a deeper theoretical understanding of the scientific and medical underpinnings of CAR-T therapies, this list shows that the operational and clinical handling of the different steps require advanced practical skills and expertise. In close alignment with regulatory authorities, a specialised mechanism for the selection of CAR-T treatment centres as well as for the training and qualification of these treatment centres has been developed. During this process, Novartis expert teams collaborate in a unique, novel way with many different departments in hospitals, including aphaeresis centres, hospital pharmacies, physicians and nurses handling the patient's treatment and the hospital's legal departments.

Novartis provides to the treatment centres as well as to the associated aphaeresis centres a unique and highly specialised technical, quality and operational support. A range of cross-divisional experts forms the so-called 'hospital onboarding team'. On the level of the aphaeresis units and the cell therapy laboratories, the support includes focused technical operations expertise on the cell collection, cell processing and cryopreservation and logistics operations. This training is matched according to the Novartis' CAR-T product specifications. Quality experts ensure that the related activities comply with all the applicable regulations and standards.

The treatment centres are also supported with operational experts. Their task is to ensure that all steps in the end-to-end qualification process are fulfilled properly. They provide appropriate trainings on ensuring an undisrupted chain of identity and on ordering management using Novartis' proprietary CellChain platform. They also train staff at the treatment centres on all steps of the CAR-T product's risk management plan (European Medicines Agency, 2018). Trainings are conducted in partnership with the medical teams and organised according to locally approved Health Authority materials.

The support delivered to the centres goes beyond training and qualification and also includes project management support helping to ensure that all the steps of the mandatory centre qualification progress are fulfilled and that potential challenges and gaps are addressed and solved. On a case-by-case basis, this may include audits and appropriate discussions with local competent authorities.

As the Novartis onboarding teams work across multiple countries and geographies, they consolidate extensive operational know-how to share with centres in all countries. Thus, they can help centres not only implementing CAR-T but also progressively improving the efficiency of their operations to continuously improve their 'vein-to-vein' processes and the safe delivery of therapy to patients. Once the centre qualification process is concluded, the Novartis support does not end. Subject matter experts remain available to support in technical, quality and operational aspects when centres 'go live', creating a new level of partnership between manufacturers and hospitals. The complexity around CAR-T therapies is significant, and it truly takes a community-based approach to help the treatment ecosystem grow and develop. As a pioneer in this area, Novartis is committed to facilitate this sector journey as physicians tackle the uncharted territory of CAR-T medicine through offering preceptorships, webinars and frequent data sharing to the healthcare community. All of that requires a new level of partnership and collaboration between the manufacturer and hospitals to create solutions for known and new challenges in this truly uncharted area.

Ultimately, this complexity also explains why the commercial launch of CAR-T therapies needs to follow a staged approach. To be able to offer such treatments, a sophisticated infrastructure needs to exist on a country level, which includes (but is not limited to) treatment centres which have the appropriate equipment, facilities,

experience and staff to manage patients and technology. Novartis is committed to help building this ecosystem of innovation.

THE VALUE OF CAR-T CELL THERAPIES

CAR-T therapies are spearheading the field of commercial cell and gene therapies. They contrast with continuously dosed therapies where the annual costs may be lower, but the accumulated long-term expenses may sum up considerably. The key principles of industry's pricing strategies in this field are currently subject to substantial public and expert debate. As some authors correctly outline (e.g., Faulkner et al.), manufacturing and delivery costs of some advanced therapies are significant and can 'approach [healthcare systems] willingness to pay, even without including a profit margin for the manufacturer' (Spinner et al., 2019). In the public debate, there is sometimes a push to specify the exact costs for the research and development phase, plus the manufacturing and distribution process, on which to base the medicine's price. However, such 'cost-plus' pricing models suffer from key weaknesses.

Firstly, the complexity of today's biomedical research and development is prohibitive to assigning definite and precise numbers to the research and development expenditures for a single project or medicine. This is especially true for highly innovative medicines such as CAR-T therapies, where innovators take highly risky investment decisions at almost every step of the process.

The second weakness of such models relates to the inherent logic of today's modern market principles. Almost all products and services offered and sold are priced on the value individuals or societies assign to them. Neither a physician's salary is defined by the personal investment in his/her education and skills nor does the price of a car breakdown into the engineering and design investment plus the costs of manufacturing. We live in a society in which different stakeholders jointly define a 'fair' price in the system. In the case of pharmaceuticals, this price ultimately needs to be balanced with the legitimate interests of multiple, equally important stakeholders, most importantly of patients, clinicians/hospitals, healthcare systems and society.

Thirdly, a pricing system based on costs or on a 'fixed margin' for the manufacturer would reward indifferently a drug targeting a high medical need area and a 'me-too' medicine in an already well-explored indication. This would not provide any incentive for manufacturers to take high-risk research and development opportunities, which produce revolutionary technologies targeting high medical need, such as CAR-T therapy. Also, this approach does not reward efficiency. Let's look at a short example:

> Company A is highly efficient and innovative. It spends amount x to develop a drug for disease y.
>
> Company B is inefficient and wasteful. It needs 10 times amount x to develop a me-too drug for disease y.

In a 'cost-plus' model, company B could charge a higher price – something that society should not support.

Patient and Clinical Value

On the most fundamental level, the product price needs to reflect the value a new intervention delivers to individual patients and their families or caregivers. Clinical outcomes observed in interventional clinical trials, observational studies and patient-reported outcomes attempt to measure this value.

A medicine's value relates to the clinical value it delivers, both to the patient population and the hospital and medical community. Although there is quite some overlap between clinical and patient value, they are not truly identical, and some of the differences are in fact striking. A good example is the clinical and patient value CAR-T therapies brought to the paediatric ALL patient population. On a purely clinical outcome level, CAR-T therapies and successful stem cell transplants may lead to similar outcomes when measured by full remission and overall survival rates. However, from a patient and caregiver perspective, both interventions may have significantly different value parameters. The treatment cycle of a stem cell transplant involves induction chemotherapy, high-dose chemotherapy, the transplantation procedure and any potential follow-up complications, which may, in its entirety, last many months and result in long hospitalisation and recovery periods. These are usually prohibitive to a normal daily life, including school attendance and interactions with other children or teenagers. Moreover, the treatment may have severe side effects and long-lasting impact such as women in their reproductive age who may lose fertility. On the contrary, a CAR-T treatment cycle is comparably short, and patients who respond completely can return to a normal life shortly after reinfusion. For a child's healthy development, the difference between several months or a few weeks of absence from a normal life is significant, and this also significantly impacts their parent's or caregiver's lives.

Healthcare Systems and Societal Value

A significant value category is the impact of a new intervention on the utilisation of healthcare resources and its overall efficiency. One-time treatments such as CAR-T therapy or other recent gene therapies produce long-term therapeutic effects on diseases with a high burden: the avoidance of hospitalisation, medication and use of other health- and social-care services could deliver a high value to healthcare systems with overall cost savings.

In haematologic malignancies, CAR-T therapies could help to avoid other costly interventions such as stem cell transplantations. In the United States, ICER found CAR-T therapies to be cost-effective at their US price for both indications. Currently, CAR-T therapies are licenced for a very small subset of patients with rare B-cell

malignancies whose tumours are either refractory to existing treatment protocols or who have suffered two or more relapses. These patients are terminally ill and usually out of other medical options. Because of the very low number of these patients, the overall cost impact of the treatment on healthcare systems is low to very low. It is difficult to quantify the value or avoid healthcare costs of patients who no longer need lengthy and costly care – the current alternative for such patients who typically have a life expectancy of under 1 year.

Finally, beyond direct healthcare costs, CAR-T therapies also provide societal value, with the potential of returning to a 'normal', productive life. Children are able to go back to school, learn a skill and have a productive life, whereas adults are able to return to work and resume a normal life. Families and caregivers, who have a deep emotional involvement and who sometimes stop working to manage the heavy treatment of their relative, can also resume their lives.

Although CAR-T therapies offer significant value for patients and healthcare systems, they can create challenges for payers because healthcare budgets are often rigidly separated into cost categories, making it difficult to realise savings across budget lines. Also, in many countries, healthcare budgets are set year-after-year, making it difficult to account for the potentially long-term benefit for the patients. This can even be true for therapies that are considered cost-effective by health technology assessment bodies. Innovative financing models that allow cost off-sets across budget lines and move beyond annual budgets and focus on long-term results may be needed to fully realise the cost-saving potential of these innovative therapies.

The launch of the first two CAR-T therapies, as well as the advent of a range of gene therapies in other therapeutic areas such as ophthalmology and neuroscience, has triggered a vivid public and expert debate on pricing and payment models for cell and gene therapies. The terminology in this area is still evolving with one and the same term often being used in very different ways. For example, some define 'outcomes-based' payment as a binary model where failing or missing a predefined clinical outcome (e.g., full remission of a tumour) either leads to no payment at all or to full list price payment. Others understand 'outcome-based' payments as modular concepts, with more flexibility: partial payment at partial remission or milestone payments at certain predefined points in time or evolving prices based on confirmation of long-term or real-world evidence.

During the early phase of commercialising a CAR-T therapy across Europe, Novartis saw how vague current terminology is, despite industry and other stakeholders having been discussing innovative pricing models and outcome-based approaches for a long time. This chapter is being written at an exciting point in time, as progress in the debate is truly happening while 'we speak'. The following section aims to bring some structure and clarity to this debate. Although the discussion is a global one, this section will mainly use learning from Europe and neighbouring countries.

PAYMENT MODELS FOR CELL AND GENE THERAPIES

Today's marketed CAR-T therapies have a public price across the European Union Member States and adjacent countries such as Switzerland, Norway and Israel set in a narrow range. In the case of Novartis' therapy, the price in Europe is in the range of €320,000 for both indications. In the United States, the pALL price is $475,000 for those with ALL and $373,000 for DLBCL (the US system is permissive of indication-based pricing).

To commercialise the therapy in Europe alone, negotiations have to take place in more than 30 countries, which do not only differ by population size and economic power but also represent a great variety in healthcare systems, payer landscape, as well as societal, historical and political traditions.

Obviously, a broad range of payment models for innovative medicines has evolved over the last decades, which are summarised in Table 28.1. However, these models have historically been used mostly for medium- to long-term interventions and have not yet been tested for one-time, high-value medicines such as CAR-T or cell and gene therapies.

This is not the place to describe the payment models in detail, as there is a significant body of expert literature to refer to (Carr and Bradshaw, 2016; Brennan and Wilson, 2014; Ferrario, 2015). As a pioneer in commercialising a CAR-T therapy across different markets, Novartis strives to be a partner to all relevant stakeholders to find local pricing and reimbursement solutions that match the key needs of all parties.

Although this journey continues, Novartis is learning on a daily basis how different healthcare system can have specific framework conditions that profoundly impact payment modalities for therapies that potentially deliver substantial, multiyear value with a single administration.

For example, markets with multiple private payers, where patients can switch their insurance, may struggle with an annuity payment model because of rather simple operational issues. Annuity payment may also be a challenge for the many healthcare systems that manage their budget yearly.

Outcome-based risk-sharing models are propagated by many, but there is significant variability in this type of reimbursement model, and both terminology and models are evolving in real time. The lay audience may still consider outcome-based risk sharing as an 'all-or-nothing' approach, whereby payment is only due if an individual patient shows a positive outcome. Awareness on the different variations of outcome-based models needs to be improved, as well as the disproportional risk this model represents for the innovator, which, again, needs to be reflected in the price. In the case of CAR-T therapy (or other single-administration therapies), only realistic indications are put forward, where a highly predictable clinical outcome can be measured in reasonable proximity to the treatment. Although Novartis pioneered this model for pALL in the United States, the special situation in single-payer markets encouraged the introduction of other outcome-based risk-sharing models.

Table 28.1 Simplified Overview on Payment Models for Cell and Gene Therapies.

Category	Subcategory	Key features	Practicability
Financial-based risk sharing	List price rebates	Rebates applied either as reduced invoice at point of purchase or as a later payback to the health insurer (on individual or patient-cohort basis).	Common model, but may not address the specific pricing challenges of a one-time therapy with potential long-term action like CAR-T.
	Annuity	Can be used as standalone or in combination with other models. May decrease manufacturer profitability.	Require multiyear healthcare budget planning.
	Reinsurance		Relevant for smaller health insurers and/or rare conditions to manage potential spikes in expenses.
Outcome-based risk sharing or pay for performance	Pay for positive outcome only	'All-or-nothing' payment model, full list price due if the outcome of the treatment is positive at time x, otherwise no payment at all.	Requires easy-to-monitor and highly predictable clinical outcomes. All risk with manufacturer, the success price should reflect the value of the successful treatment only.
	Risk-sharing price depending on outcome	Payment modified in accordance with certain predefined treatment outcome. Different variations are possible, e.g., • full list price on treatment success at time a, reduced price otherwise, • instalments conditional to certain predefined outcomes.	The lower the nonrefundable upfront payment, the higher the risk born by the manufacturer.
	Risk-sharing price depending on evidence development.	Price potentially evolving based on future evidence, e.g., long-term clinical trial data or real-world effectiveness from registries	Price may evolve downwards or upwards.

The most relevant learning to share at this point in time – roughly 18-month post-regulatory approval of the first CAR-T therapy for two distinct indications – is the need to engage early on with key stakeholders with a mindset of openness and collaboration. CAR-T and cell and gene therapies are new to all involved and industry needs to take the concerns of stakeholders seriously. These concerns are multifold and broad, from questions

on the long-term efficacy of the therapies, comparability of therapies when existing study results mainly originate from single-arm trials, up to affordability questions and the overall impact on healthcare systems as more cell and gene therapies are developed. The landscape is evolving, and today's pricing models may not be the models for the next wave of innovation. It is not unrealistic to anticipate evolution in the health economic and payment model space, and any responsible innovator must be prepared to participate as a trusted partner in the necessary discussions around this theme. At this point in time, this requires sharing experiences and challenges through existing platforms such as industry associations, policy and stakeholder congresses and events and scientific publications such as this book. We believe that significant progress has already been achieved; however, the journey will need to continue, especially outside of Europe and the United States.

ACCESS AND RESPONSIBILITY – A PRIVATE SECTOR PERSPECTIVE

As Faulkner et al. mentions in Chapter 27 of this book, different-sized private companies are subject to different internal and external factors, which frame their price-setting strategies. Smaller or single-product companies are more dependent on immediate or short-term returns on investment to 'fund future research development, be considered viable as a partner for acquisition or support an initial public offering'. (Spinner et al., 2019) For large enterprises with a substantial portfolio of in-market products, as well as a strong and viable pipeline, such immediate pressure is less relevant. Pioneering innovations, such as the first-ever marketed CAR-T therapy, are embedded in Novartis' long-term strategic approach, which aims to transform not only the medical management of cancer or severe inherited disease but also the societal and healthcare system conditions for embracing and rewarding innovation.

This strategic approach to exploring and building the market for a new class of therapies comes with multidimensional responsibility. In the case of pricing innovative medicines, a private company's actions must be in line with at least four areas of responsibility:

1. Patient responsibility
2. Clinical responsibility
3. Shareholder responsibility
4. Societal responsibility and society's responsibility

Patient Responsibility

Acting responsibly towards patients is of utmost importance to Novartis. Never before has industry been as close to the patient as in the area of CAR-T therapy, as shown earlier. The patient is at the beginning and end of each single CAR-T batch, and a lot is learnt from individual patient case studies, which Novartis experienced through the manifold interactions with treating physicians.

Patients should have access to safe and effective medicines. For any pharmaceutical product, manufacturers must collaborate with many different stakeholders to enable this. When it comes to pricing, the industry's role in the stakeholder network varies from country to country and healthcare system to healthcare system. As a rule of thumb, industry's patient responsibility is the largest in markets where individual healthcare coverage is low and patient access to innovative medicines requires partial or full 'out-of-pocket' payments.

Patient responsibility has two dimensions; there is the immediate responsibility towards patients who are in dire need of immediate therapy and the long-term responsibility towards future patients who may need either existing or next-generation CAR-T therapies in the months and years to come. In some scenarios, these two spheres can come into conflict, as the following hypothetical case study exemplifies.

> Case study A*: A company with a CAR-T therapy in its pipeline receives regulatory approval in a highly developed market. A public authority sets prices for medicines. For in-hospital therapies, this process can take many months. As the company starts price negotiations, several terminally ill patients need immediate treatment access. While their insurers deny coverage of the treatment costs, patients may suffer, and the manufacturer is faced with a very high public reputation risk.*

If the medicine were a small molecule that needs to be taken regularly over a longer time, the solution could be simple: offering the drug for free until a reimbursement agreement is found.

However, in the case of CAR-T therapies (or other lifesaving gene therapies), the situation is far more complex. CAR-T manufacturing and delivery is highly complex and requires significant (financial and nonfinancial) resources. Offering the therapy for free to a range of patients might undermine the company's ability to operate. Initial financial losses on individual patients cannot be compensated with future sales of the medicine to these patients, as CAR-T therapies are one-time interventions.

In the hypothetical case study, the company faces a situation where every possible decision leads to an undesirable outcome. In order to act responsibly towards the patient, the therapy is offered for free to patients in immediate need. However, this puts the medicine's commercial viability and the company's business model at risk – both are essential to fulfil the company's responsibility towards future patients.

As the case exemplifies, current well-established schemes used to navigate patient access situations are modelled for traditional pharmaceuticals and do not fit for one-time, potentially curative therapies. This is an area where continuous focus and innovation by all stakeholders is required to further enable sustainable access to these therapies for patients. Larger companies, with a strong backbone of in-market medicines and pipeline products, could absorb such demanding situations more easily than small- or medium-sized companies. They are able to give their cell and gene therapy teams the time and flexibility needed to work with all relevant stakeholders towards long-term, sustainable access solutions.

Clinical Responsibility

Clinical responsibility describes accountability towards a larger group of patients and their healthcare professionals, unlike patient responsibility, which is rather bilateral. A pharmaceutical company's responsibility is often described as its willingness and ability to deliver meaningful and substantial proof of a medicine's clinical value, usually measured by the clinical outcomes before and after regulatory approval. While for an individual patient the outcome may be binary (e.g., survival at time x is an either/or outcome), the cohort outcome describes a statistical relationship (e.g., survival at time x is achieved by y%) and helps physicians and patients to take informed decisions about treatment options. The medicine's price and the demand for substantiated proof of clinical value directly correlate. In the area of CAR-T therapy, the proof of clinical value has a strong time component, as it is generated through a single intervention with a long-term effect. Commercial CAR-T therapies are still in their infancy, so clinical value data sets are limited by the relatively few patients treated, and the length of time outcomes have been monitored. Although the clinical phase of CAR-T therapies produced impressive results that accelerated their approval, payers are wary of the lack of long-term results. It is essential to appreciate that this is not a weakness of these therapies but an intrinsic characteristic of any breakthrough innovation. Moreover, market authorisation by regulatory bodies such as the FDA and EMA is dependent on quality, safety and efficacy, and not on cost-effectiveness, for which criteria are neither defined nor assessed; this has led to, what some payers consider, an 'evidence gap'. Thus, clinical responsibility, as it relates to pricing, includes the willingness and ability of a private company to continuously build and share evidence on a medicine's performance in both clinical trials and real-world settings and to adjust their pricing regime in line with emerging data.

Shareholder Responsibility

Since the end of World War II, the commercial production of pharmaceuticals has revolutionised modern medicine. Spearheaded by the ability to manufacture antibiotics at industrial scale, the following decades witnessed groundbreaking innovation in almost all major disease areas. As science is about to enter a new era of medicine, with cell and gene therapies maturing from experimental treatments for very few patients in clinical research programmes to commercially available therapies for larger patient populations, it is also justified to briefly reflect on the central role investors have played in this historical journey. Up to this moment, no major medicine has been developed in the public sector alone. There are many reasons for this, but the preclinical and clinical development of an innovative therapy in multicentre, global clinical trials is a hugely complex and costly enterprise which requires multiple expert skill sets that are usually less relevant to succeed in the academic setting. Also, most Western countries aim for a stringent separation

of public, non–profit-oriented research and private sector activities, where profitability and creation of new jobs is seen as a value in itself. The establishment of special intellectual licencing or start-up facilitation offices in most major universities pays tribute to this societally accepted separation.

Similar to most major pharmaceutical companies, Novartis is a publicly traded company. The investment decisions of the leadership must be in line with the justified expectations from the investor's community. Although shareholders of a pharmaceutical company are well aware that research and development investments have a higher risk of failure compared with other sectors, they mainly base their investment decisions on calculated assumptions of a return on this investment, may it be a rising of the share price or attractive annual dividend. Within the stock markets, Novartis competes not only with other pharmaceutical companies but also with all publicly traded companies for the trust and support of its current and future investors.

As a result, investors' interests have to be taken into account in every major decision, including decisions on the pricing of its products. To the benefit of highly innovative platforms such as CAR-T therapies, Novartis has a rather broad portfolio in which more conventional therapies in other disease areas such as skin disorders, ophthalmology or cardiovascular provide a very solid basis for the company. This gives the leadership the breath and opportunity to pioneer in new areas, where there is a lot of unchartered territory that needs to be explored before CAR-T therapies (or other cell and gene therapies) can broadly benefit society as well as shareholders.

Societal Responsibility and Society's Responsibility

Pharmaceutical companies operate in a highly complex environment and offer intrinsically 'ethical' products to society. A potentially lifesaving medicine has a very different status to a car or a kitchen. For that reason, developed societies have installed healthcare systems, many of which operate on the solidarity principle, where the protection of the sick and vulnerable is a joint public good.

One of the many advantages these systems offer to the individual is that prices of healthcare goods and services are negotiated between the goods/service provider and a public or private organisation, i.e., the vulnerable individual patient is not part of this discussion (though increasingly, patient organisations demand a voice). In many countries, payers are governmental or public organisations, but in other countries, payers are private entities or a mix of public and private institutions.

A solid and functioning healthcare system is one of the most important components of a modern state. Many argue that the existence of and access to such a healthcare system marks the difference between developed and developing countries. Preserving and protecting the functionality of healthcare systems is thus an imperative responsibility of all stakeholders.

Although pharmaceutical expenditures constitute only a small proportion of overall healthcare costs, such as 11.4% in the United Kingdom, 13.8% in Switzerland and 6.6% in Denmark (OECD Data, 2017), the advent of single-treatment, potentially curative, cell and gene therapies cause legitimate concerns about their potential to disrupt well-functioning systems.

On the level of a single treatment, such concerns seem rather unjustified. In the case of currently licenced CAR-T therapies, the overall systems impact is limited as the number of eligible patients is very small. Novartis strongly believes that to truly subscribe to its societal responsibility, its approach to pricing and reimbursement has to take the legitimate medium- and long-term concerns of payers, policy makers and society into consideration. In practical terms, this means carefully balancing patient, clinical, society and shareholder responsibility in an open-minded dialogue. Novartis will negotiate solutions to patient access on a country-by-country, healthcare system by healthcare system basis – bearing in mind that any solution may set a precedent for the next wave of cell and gene therapies, so it has to work beyond the actual negotiation.

But societal responsibility is not a one-way road. Today's health issues cannot be solved by one organisation alone. Private companies, governments, nongovernmental organisations and other stakeholders all have a role to play in creating sustainable solutions.

While Novartis will do its utmost to advocate for, and support change in, healthcare policy and healthcare system design to help remove barriers to access, change will be needed in many different areas as the field continues to evolve. This requires an open mindset and the willingness to discuss, learn and adapt by all who contribute to building the future of medicine and healthcare systems. It is a joint responsibility to look for solutions that work for all. Very often, this will be a compromise, which is the nature of democracy. Policy makers will need to deepen their understanding about the nature of science and medicine. Current CAR-T therapies are often criticised for failing to deliver long-term data or head-to-head comparisons with the standard of care. Both arguments are true. There are no long-term data available for today's CAR-T therapies, and they have not been developed in head-to-head trials. But this a weakness by design mandated by our ethical standards and an intrinsic characteristic of breakthrough innovation. FDA, EMA and other authorities granted these therapies' accelerated review because the clinical data were so strong that withholding them from a patient community in dire need of new treatment options was considered unethical. Journalists, payers and regulators should appreciate that it is not possible to have long-term follow-up data in such a situation. They should also appreciate that the first generation of clinical trials in CAR-T therapies provided potential solutions for terminally ill patients who ran out of other medical options. Again, in such a situation, the absence of a head-to-head trial against the standard of care is not a weakness by design but an intrinsic characteristic of the innovation under investigation.

The needs of patients, society and the industry are, in the end, quite similar. It is true innovation to conquer diseases for which currently no – or no satisfactory – treatment options exist. This innovation must be delivered in a sustainable way, whereby patients in need have access to safe and effective therapies, society can fund this in a way that healthcare systems are not disrupted and the industry can deliver a justified return on investment to its shareholders to ensure the sector is attractive in the long term for the investment it needs. In the advent of cell and gene therapies, trusted collaboration of all stakeholders is more important than ever before.

PERSPECTIVES

Commercial CAR-T therapies have delivered hope and sustained overall survival to patients who up to now had very short life prognoses of under 1 year using prior existing standards of therapy. The hope that has been instilled in many cancer patients is high, and it is supported by the fact that the therapies are delivered as one-time infusions rather than as chronic treatments. At the same time, the pioneering nature of the therapies has uncovered the need to resolve newly apparent gaps and unresolved issues in existing laws and regulations – these must be addressed responsibly by all stakeholders to create fertile ground for future innovation in cell and gene therapies where CAR-T therapies are frontrunners for more high-value, one-time therapies with potential long-term efficacy.

To ensure a successful and responsible market access for breakthrough innovation, true collaboration with regulators and policy makers is of paramount importance. Many relate this first and foremost to the value and access discussions – we will address these separately. But in fact, there are many other areas that are impacted and where regulatory or legislative adaptations may be necessary.

Medical and clinical field: It is critical to continue to monitor the long-term safety and efficacy of these interventions. Similar to other CAR-T therapies, the Novartis therapy was developed in single-arm clinical studies, and long-term data are being generated while the medicine is already approved. Also, in some countries, it is challenging to start CAR-T clinical trials as local regulatory frameworks are not fully prepared for this kind of innovation.

Novartis has partnered with regulatory authorities to codevelop a system for the generation of long-term data through a global multicentre, prospective, observational and noninterventional study. It will collect 15-year safety and effectiveness follow-up assessment of patients who underwent a CAR-T treatment with our commercial therapy. The setup of this study required collaboration with academic institutions that support the study data collection. The databases will be maintained separately in each region, and data integration and data cleaning is handled through a collaboration with a contract research organisation. The study will be a key to help understand the long-term benefit

of CAR-T therapies to patients in a true real-world setting. This will require more uniform assessment criteria. To give one tangible example, currently marketed CAR-T therapies rely on different grading schemes to assess the severity of CRS, one of the most relevant treatment side effects. This makes direct comparisons of the therapies challenging. Novartis is committed to working with regulators, academia and the growing CAR-T industry community to close such gaps.

Complex approval processes: Currently, the approval of CAR-T medicines is based on three pillars: a deep review and approval of the manufacturing process, an approval of the final product and an approval of the risk management plan and treatment accompanying measurements such as hospital qualification. While all three pillars are equally important for the first generation of CAR-T therapies, the focus may need to shift as technology and medical experience mature. For example, the very granular regulation of the manufacturing process may become less relevant over time. Such focus from process-to-product approval will take time but will be essential to foster faster innovation in the manufacturing process with the ultimate objective to streamline the manufacturing time. Focussing on cellular molecular footprints to validate a cell-based product is a very novel approach that is not yet validated or approved and may result in a valid approach.

Local and other regulations: While long-term data collection and regulatory approval processes are rather global topics, other areas of policy collaboration are equally relevant on a regional or local level. Seemingly, small topics such as export licences for aphaeresis material may become significant once commercialisation starts. For example, some countries regulate the cell material as human tissue, others as blood product – which has direct impact on applicable regulations as it is either the manufacturer or the treatment centre that needs to apply for the export licence. In some cases, this may have a negative impact on the critical turnaround time for the benefit of patients.

The same applies to local regulatory requirements on the treatment centres, quality controls for the final product and sometimes even custom release processes. From a patient perspective, it is difficult to understand that an organ aimed for transplant may sometimes pass customs faster than an equally important, potentially lifesaving CAR-T cell suspension of a patient's own cells.

Data privacy: From an innovator perspective, data privacy laws are business critical in CAR-T therapies as a significant amount of sensible patient data are part of the whole end-to-end manufacturing and delivery process, and these data are shared across different legislations. For example, in the case of Europe, a patient's cells may be withdrawn in a non-EU Member State, transferred on the ground to the next airport in an EU Member State, exported to the United States, manufactured and reimported into an EU Member state and back to a non-EU member state treatment centre. Although the EU has set a stringent common legislative framework with the General Data Protection Regulation, implementation on a local level differs, e.g., in many European countries, a web-based database containing patient information still requires local (regulatory) review and approval.

These examples show that harmonisation to the most appropriate standards is critical, especially in complex clusters with many small- and medium-sized countries, such as in Europe or the United States and Asia with a different legal framework.

Cross-border access: As the rollout of CAR-T therapies proceeds in countries with qualified treatment centres, patients from countries lacking hospitals with adequate training will likely travel to receive treatment. This area is not well developed, especially for patients who rely on their healthcare system to cover the costs. Few regions have legislation comparable with the EU cross-border directive, yet travelling to a treatment centre may be fundamentally important for many patients across the globe. A deeper understanding of the underlying mechanisms and principles of existing cross-border healthcare pathways is a key undertaking in Europe. Although a legislative pathway exists, many operational details need to be identified and addressed by the sending and the receiving country. With Novartis pioneering the commercialisation of this therapy in global markets, these challenges increase as no established cross-border pathway exists in regions such as Asia-Pacific, yet patients from Southeast Asia may seek treatment access in Japan or Australia, where the therapy is approved, and hospitals are being qualified at this very point in time.

Looking ahead: Today, the patient communities are starting to realise the transformative potential of CAR-T therapies in haematological malignancies while clamouring for faster development against solid tumours. At the same time, many stakeholders in the healthcare policy area struggle to fully appreciate the intrinsic complexity of CAR-T and to find ways to streamline their rollout. Trade associations and expert groups are in early stages of their learning curves, and even the very small group of leading innovators, such as Novartis, is only beginning to understand the full picture. More time and platforms are needed to share their learnings on a broader base and collaboratively tackle the open issues. Novartis is currently actively partnering with some key platforms to advance this dialogue in close collaborations with all who need to contribute, including not only industry peers, regulators and policy makers but also patients and representatives of the civil society. This dialogue is of critical importance, and while it is ongoing, there is a shared responsibility to ensure that patients who are eligible for treatment are not negatively affected by today's debates about tomorrow.

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