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Transfer Pricing Considerations in the Age of Precision Medicine

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Editor's Note: In this article, the authors examine the differences of CAR T therapies from traditional pharmaceutical products and explore the associated transfer pricing considerations.

INTRODUCTION

Precision medicine (PM) is fundamentally transforming the healthcare and life sciences (HCLS) industry. Often viewed as the future of medicine, PM is becoming increasingly important to stakeholders across the entire HCLS ecosystem, including academic medical centers, diagnostics and biopharma companies, laboratories, healthcare providers, payers, and data providers. These stakeholders recognize that medicine is moving from a ''one-size-fits-all'' mentality to an approach that diagnoses and treats disease tailored to an individual's genes, environment, and lifestyle. The importance of PM is moving beyond the vanguard of oncology to other disease areas such as neurology and autoimmune diseases.

In this article, we focus on chimeric antigen receptor T-cell (CAR T) therapy, a type of cell and gene therapy (C&GT) that represents one of the most exciting and high-profile areas of PM, and an area that has seen major investments in recent years as these technologies have, in some cases, had curative outcomes for patients. At the time of writing, there were six approved CAR T products in the United States.[1] However, the American Society for Cell + Gene Therapy cited a listing of more than 800 different types of cell therapies in clinical trials and more than 8,000 active, or actively recruiting, clinical trials for cell therapies on ClinicalTrials.gov.[2] Reflective of this excitement, many big pharma companies have made significant investments into their CAR T capabilities in recent years, from outright mergers and acquisitions (M&As) in order to access technologies and platforms, to large capital investments in manufacturing facilities. CAR T products are currently marketed and are being investigated in clinical trials for many diseases where patients have no other treatment options.

This article discusses the disruption caused by CAR T to standard business models in the life sciences industry and its implications for transfer pricing.

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This content outlines initial considerations meriting further consultation with life sciences organizations, healthcare organizations, clinicians, and legal advisors to explore feasibility and risks.

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[1] U.S. Food & Drug Admin., Approved Cellular and Gene Therapy Products (rev. Aug. 17, 2022).

[2] Am. Soc'y for Gene + Cell Therapy, Gene and Cell Therapy FAQ's.

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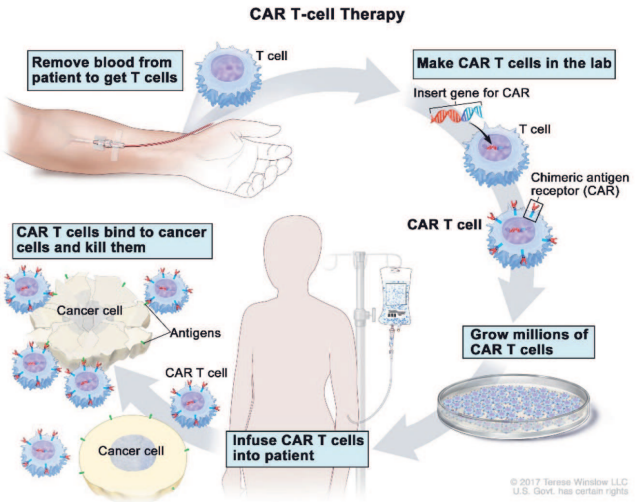
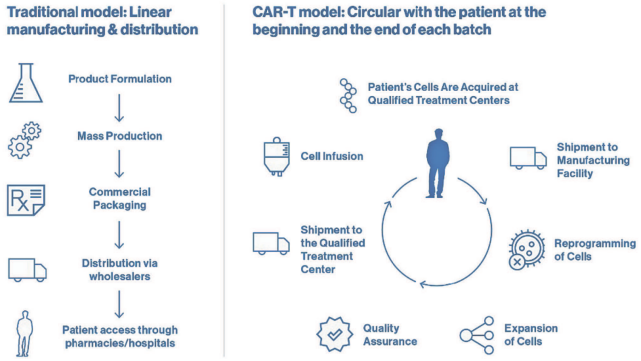
OVERVIEW OF CAR T THERAPY

It is useful to start with an appreciation of how CAR T works. Many cancers have developed mechanisms to ''hide'' from the patient's immune system, rendering the immune system unable to recognize and kill the cancer. CAR T works by re-engineering a specific cancer-fighting white blood cell called a T-cell. Simply put, a portion of a patient's (or a donor's) blood is extracted in a hospital and the T-cells are separated from the blood. The T-cells are then shipped to a manufacturing facility where a cancer-recognizing gene is introduced using a harmless virus. The T-cell turns this gene into a protein that sits on the surface of the T-cell, allowing it to recognize and kill the cancer. These ''genetically engineered'' CAR T cells are expanded and then shipped back to the hospital where they are infused into the patient. If the T-cells come directly from the patient, this is known as autologous, whereas allogeneic CAR T means a donor has given their T-cells to be used in someone else. The schematic below illustrates the vein-to-vein process for autologous CAR T.[3]



CAR T BUSINESS MODEL

The overall cell and gene technologies, including CAR T, are leading to significant changes in established HCLS business models. The following figure provides a stylized depiction of value chains of traditional pharma (which deals with small molecules and biologics such as proteins and monoclonal antibodies) vs. the autologous CAR T process, which is perhaps the most complex of the C&GTs.



Source: Emanuele Ostuni et al., Chapter 28 — Commercialising CAR T Therapies: The Evolution of a Revolution; Editor(s): Alain A. Vertès et al., Second Generation Cell and Gene-based Therapies, Academic Press, 2020, pp. 747--775, ISBN 9780128120347.

Unlike the traditional pharma business model, the CAR T process sees far greater touchpoints between the patient and other key stakeholders in the ecosystem, with the patient as a focal point in the manufacturing processes. Multiple parties — pharmaceutical companies, apheresis centers, hospitals, or treatment centers, as well as those companies' manufacturing vectors — need to work together to create awareness and acceptance of these therapies, as well as deliver them. In CAR T, the patient is not just a consumer of product as in the traditional pharma model but is central to the manufacturing of the product by contributing the raw materials in the form of their T-cells; in essence, the patient *is* the product.

Key Players in the CAR T Business Model

The growth in CAR T has led to the emergence of new types of players that are involved in the manufacturing and delivery of these complex therapies. An important note is that there are a vast number of raw materials and technologies required to make CAR T, many of which are made by small start-ups, and a significant number that have been spun out of academia. This makes it very challenging for scale to be achieved when moving from clinical to commercial supply as not all these suppliers can meet the increasing demand being placed on them by more and more pharma companies. Some of the prominent players include:

- **Academic medical centers (AMCs)**: At the moment, given the specialized nature of the treatment and the serious side-effects that can arise, CAR T therapy is given in specialized hospitals called academic medical centers. As such, patients often need to travel long distances for treatment, as only these AMCs are equipped with the infrastructure to successfully extract the T-cells, administer the therapy, and monitor the patients.

[3] Nat'l Cancer Inst., CAR T-cell therapy (definition).

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- **Specialized contract development and manufacturing organizations (CDMOs)**: There are many types of specialized CDMOs involved in making the raw materials for CAR T, from plasmid and cytokine manufacturers, to those that manufacture the virus that is used to reprogram the T-cells. While CDMOs have supported the development and manufacture of small molecules and biologics for decades, the manufacture of the input materials for CAR T is highly specialized.
- **Information technology infrastructure enablers**: These players provide tools to facilitate the collection, breakdown and analysis of disparate patient, tissue, transport, manufacturing, and health outcomes data. This includes the tracing and tracking of every step during the ''vein-to-vein'' process in autologous CAR T therapies.

CAR T vs. 'Traditional' Therapies: Functional Considerations

CAR T is one of the most complex and technologically advanced therapies ever developed by the biopharmaceutical industry. This has important considerations for various functions in the biopharma company.

Research & Development

Like traditional pharma, the development of CAR T follows phased discovery and animal and human clinical trials, albeit some aspects of timing and required resources may differ significantly, and the U.S. Food and Drug Administration (FDA) regulates CAR T therapies as drugs. However, while common ground remains with traditional medicine, much is different with the CAR T development process.

Recruiting and managing the right patient population for clinical trials can be a significantly greater challenge for CAR T development given the narrower target patient populations, who typically have rare types of cancers and have undergone several types of traditional treatments (e.g., chemotherapy).

Additionally, managing the clinical trial process can be challenging. Unlike traditional therapies, CAR T requires significant patient engagement and support during a much longer treatment process. CAR T clinical trials also require specialized capabilities, such as cell handling and sterile environments including negative pressure hoods. Currently, there is a shortage of experienced physicians and centers that are equipped to run CAR T trials. As a result, clinical trials are largely conducted at academic research facilities that meet specialized standards.[4]

Further, at the same time as the FDA is creating new designations to accelerate clinical trials, regulatory standards have tightened. For example, in 2020, several companies were forced to delay their development timelines after the FDA asked for more information about their production processes.[5] The approval granted to many companies is also conditional, as regulatory agencies will request additional clinical data in the future.

Commercialization

''One-time curative therapies'' such as CAR T that are considered to substantially reduce societal health care costs can carry commensurately significant pricing. For the CAR T therapies that have been approved in the United States, total cost, including the cost for the therapy itself and that associated with specialized care centers and physicians to administer the treatment, can be well over USD 1 million.

As a result, pricing decisions, reimbursement strategies, and patient access programs take on a more prominent role. For example, some companies have proposed spreading the payments into several installments and entering into value-based payment agreements, meaning that payers pay only if the therapy delivers on its promise. Even so, it may still be a challenging process to reach an agreement on the price with the relevant authorities.

Manufacturing and Supply Chain

CAR T manufacturing, and subsequently the supply chain and distribution of CAR T therapies, are very different from the processes of most small molecules and biologics because its start and end points (for the autologous procedure) are a patient's own cells (vein-to-vein process). In all cases, the patient cells are harvested at clinical sites or specialized treatment centers and need to be transported under special conditions (both from a temperature/sterility and patient security perspective) to the manufacturing site or laboratory. Following the timely manufacture, which involves the isolation, transformation, and expansion of viable cells, the sample would then need to be securely transferred back to the treatment center in a timely manner to administer the therapy.

The success of this time-dependent value chain is reliant on fine-tuning the product and information exchange between a number of functions at the manu-

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[4] Sanjay Srivastava, *How Cell and Gene Therapy Is Transforming Healthcare*, Cell & Gene (Feb. 4, 2020).

[5] Smruthi Suryaprakash, Alexandra Teixeira, and Michael Choy, The Changing Landscape for Cell and Gene Therapy, BCG (May 5, 2021).

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facturer, and in many cases third-party partners such as raw materials providers and specialized logistics companies. This represents a fundamental shift in the way traditional pharma manufacturing and supply chain works, which would typically involve batch manufacturing and warehousing.

The biggest challenge worth noting from a manufacturing process is the limited number of players that supply raw materials (e.g., plasmids, cytokines, and viral vectors) or provide specific manufacturing equipment. This is leading to strategic acquisitions and partnerships to gain a competitive advantage or in-house development of raw material manufacturing. As the demand and the number of therapies in the market increase, investing in capacity is inevitable.

The personalized nature of CAR T therapies also presents a challenge for manufacturing as the same process may yield completely different outcomes on different patients. Patients' cells need to be engineered at certified good manufacturing practice facilities in closed systems.[6] Current processes have been conducted at a lab scale, and significant improvements are needed to produce at commercial volumes.

Distribution

CAR T also requires a radically different distribution chain from traditional pharmaceutical products.[7] Given the nature of the medicine, there is little or no inventory of finished product. The role of a wholesale distributor has diminished while the importance of logistics providers has increased.

While the life sciences industry currently has sufficient capabilities to monitor the temperature of cold chain products in transit, CAR T demands additional variables such as shock and orientation of the sample that needs to be monitored in near real-time. Companies need to be able to precisely trace and track each step of the entire vein-to-vein process. Starting from raw material collection (e.g., blood extraction) all the way through delivery, companies need to show chain of custody and track identity.[8]

There are very few couriers as of today with the capabilities to meet the rigorous quality standards, special handling and tracking requirements for shipments under refrigerated, frozen, and cryogenic conditions. With a minimum of two shipments for every patient and working with more than 500 manufacturers globally, the current capacity and capabilities of existing package and logistics service providers is tightly constrained.

Acquisitions and Partnerships

As noted, the promise of CAR T has attracted enormous investment. Deal activity in cell therapy is driven largely by deals in licensing, strategic R&D collaboration, raw material supply, and manufacturing collaborations. Larger companies have often been involved in these deals from the beginning.

A study by Gerlovin and Diesel (2020)[9] notes two striking differences in M&A deals related to C&GT with prior pharma deals:

1. Earlier deals: Unlike deals made decades ago related to monoclonal antibodies (mAbs), larger pharmaceutical companies are not waiting for the sector to become well established before pursuing deals. With mAbs, financial deals were often characterized by the acquisitions of late-stage and marketed products, significantly reducing the levels of risk. Conversely, acquisitions and other deals in the C&GT space often include entire product pipelines, platform technologies, and manufacturing capabilities with the potential to deliver significant clinical value and commercial potential.

2. Preference for partnerships and licensing deals: With the earlier deals, companies are also considering innovative deal structures to reduce risk. One key difference with respect to C&GT deals is that many companies prefer to target partnerships and licensing deals rather than mergers or acquisitions. This shift may be based in part due to the limited number of raw material providers and manufacturers and potential lack of long-term safety and efficacy data associated with many CAR T therapies.

TRANSFER PRICING CONSIDERATIONS

As discussed above, C&GTs such as CAR T therapies are having a transformative effect on life sciences business models—the value chains are evolving, new players are emerging, and the roles of existing players are changing, as are the magnitude and risk of investments required to successfully bring these therapies to market. The evolving value chains have implications for transfer pricing and will require a rethinking of certain established transfer pricing practices in the life

[7] Unless otherwise noted, this section is based on Sanjay Srivastava, *How Cell and Gene Therapy Is Transforming Healthcare*, Cell & Gene (Feb. 4, 2020).

[8] *Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs) — Guidance for Industry*, by U.S. Department of Health and Human Services, FDA, and CBER, January 2020.

[9] Lev Gerlovin and Pascale Diesel, How Cell and Gene Therapies Are Transforming Pharma Deal-Making. Pharmaphorum™ (Jan. 27, 2020).

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sciences industry. We discuss some of the emerging transfer pricing considerations below. While the discussion in earlier sections of this article focuses on CAR T therapies, most of the considerations below also apply to other types of cell and gene therapies.

Transfer Pricing Considerations in Fundamentally Different Value Chains

The transfer pricing of controlled transactions influences allocation of profits within members of a multinational enterprise (MNE) group. Increasingly, particularly since the OECD's Base Erosion and Profit Shifting (BEPS) project,[10] tax authorities have focused on the link between value creation, transfer prices, and profit allocation within the MNE group. The BEPS report titled *Aligning Transfer Pricing Outcomes with Value Creation* notes that ''[o]nce the new measures become applicable, it is expected that profits will be reported where the economic activities that generate them are carried out and where value is created.'' Formal, e.g., through value chain analyses, or informal evaluations of how value is created within a value chain is an increasing focus in transfer pricing determinations.

While the life sciences industry has by no means been static, nor has there been unanimous agreement between tax authorities and taxpayers on key value drivers in specific businesses, it is fair to say that the key drivers in traditional pharmaceutical value chains have generally been widely understood. R&D is a long, expensive, and risky process, taking an average of 10 years and, by some estimates, over USD 2 billion to get a drug from discovery to approval. Launch losses over the first few years of commercial sales could represent additional hundreds of millions of dollars of investment. Manufacturing, albeit highly regulated, has not always been viewed as a critical value driver but rather a routine cost of doing business, particularly for small molecule products.

CAR T therapies and other C&GTs are leading to a reevaluation of key value drivers in the pharma industry by transforming value chains. Some examples of questions that will need to be addressed to fully understand the associated value chains are:

- Where do activities of new players such as data aggregators, AMCs, and apheresis centers that are emerging in CAR T therapies stand in terms of relative contributions to the value chain?
- As the roles of older players change, e.g., as life sciences companies get more involved in patient care, or logistics companies play a more prominent role in the supply chain, how should their relative contributions to the value chain be assessed?

Understanding the new value chain more broadly is important to understanding the value chain contributions of various members *within* MNE groups. Application of legacy transfer pricing models without regard to the fundamentally different value chains of CAR T therapies and other C&GTs risk potential misalignment of value creation and transfer pricing outcomes. Additionally, understanding the new value chain is important for aligning or realigning value creation and transfer pricing outcomes through appropriate transfer pricing determinations for controlled transactions related to these innovative therapies.

The following sections discuss specific transfer pricing implications of disruptions in the life sciences business models, including the potential rethinking of market benchmarks, intangible property (IP) considerations, and business restructurings.

Market Benchmarks

Unlike many other industries, the life sciences industry is rich in transactional data. Taxpayers and tax authorities have, therefore, been able to rely on transactional methods for price-controlled transactions, in particular for controlled transfers of IP, with greater frequency and reliability than in many other industries. Much of the available transactional information, however, relates to the traditional pharmaceutical and biologics products. Given the different value chains of traditional life sciences business and the new therapies such as CAR T, an important question is whether the wealth of data that exists for small molecule and biologic products yields comparable benchmarks for these new therapies, or whether adjustments are required. It may take some time to build similar data sets that exists for traditional pharmaceutical and biotechnology products for C&GT products.

In addition to the use of transactional data, it is common in the life sciences industry to price or test controlled transactions involving routine services or the sale of product by benchmarking the profit margins/markups resulting from the controlled transaction against comparable company profitability. Routine comparables are widely used for transactions involving manufacturing, distribution, administrative services, and clinical trial management. With the advent of CAR Ts and the changing roles of participants in the value chain, companies need to determine whether existing approaches for benchmarking routine returns appropriately capture returns to those routine activities for such new therapies.

Finally, as noted above, certain types of activities gaining new prominence in the value chain, such as

[10] The BEPS project refers to the OECD's work to reform the international tax framework, which resulted in final reports on 15 action items in October 2015.

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logistics and medical affairs. Where controlled transactions involving such activities exist, companies need to first ask the question as to whether such activities are indeed routine in this context. If they are, and depending upon the selected transfer pricing method, companies will need to determine appropriate market benchmarks for such activities.

IP Considerations

As the value chains evolve, a key question with implications for transfer pricing is whether there are new forms of IP that are key value drivers of the business. Any new forms of IP in the C&GT business will also need to be factored into transfer pricing analyses. For example, as data and analytics gain prominence in CAR T business models, will transfer pricing need to account for those more explicitly? Similarly, manufacturing process is critical to CAR T therapies. Is there some form of manufacturing IP that needs special consideration as compared to traditional life sciences business, which also have manufacturing processes? These are just some questions that need to be considered in evaluating significant IP in these new therapies. Any controlled transactions between parties owning and using the IP will need to be appropriately transfer priced.

Additionally, one of the outcomes of the BEPS project was to require that an entity earning returns from IP perform important functions related to the development, enhancement, maintenance, protection, and exploitation (DEMPE) of the IP. Since the publishing of the BEPS reports in 2015, companies have paid particular attention to implementing this guidance in their tax and transfer pricing structures. Many companies have centralized their IP in one or two jurisdictions with DEMPE substance. As noted above, the C&GT market has been busy with many deals. Where an MNE acquires product IP and development capability in a jurisdiction different from its central IP location(s), it runs the risk of misalignment of its DEMPE substance and IP ownership if it transfers IP to the central location(s) in conformance with its transfer pricing policy. Given that the United States is currently the center of C&GT innovation, this may be a particular issue for non-U.S. headquartered companies. Companies will need to carefully consider the location of DEMPE and the treatment of IP in every new deal.

Business Restructurings

If, as anticipated by some industry watchers, certain types of C&GTs such as CAR T therapies lead to greater decentralization in business models, a key question is whether MNEs will undergo similar decentralization within their groups. While MNEs to date have tended toward centralization of key value drivers and decision-making, it remains to be seen whether CAR Ts and other innovative therapies will reverse that trend. Increasing decentralization may be associated with business restructurings, with all the accompanying tax and transfer pricing ramifications, such as new transactions to be priced and exit tax considerations.

Other Tax Considerations

This article has focused on transfer pricing implications of emerging C&GT business models, using CAR T as one example of how precision medicine is disrupting the life sciences industry and established transfer pricing approaches. It is important to note that transfer pricing is only one aspect of international taxation. The business models for these new therapies are likely to impact taxation of an MNE in various ways besides transfer pricing. Companies will need to consider all aspects of taxation to get a holistic view of the tax implications. Additionally, the transfer pricing and other tax impacts need to be considered iteratively, as transfer pricing and other tax considerations impact each other. For example, we noted above that collaboration agreements are more common in the C&GT sector. Companies will need to consider partnership implications of such collaboration agreements, which in turn may have further transfer pricing implications.

CONCLUSION

Precision medicines, including CAR Ts and other C&GTs, are transforming value chains and business models in medicine. Application of legacy transfer pricing models without regard to the fundamentally different value chains risks misalignment of value creation and transfer pricing outcomes. The evolving business models have potential implications for market benchmarks, IP considerations, and business restructurings within the realm of transfer pricing. As the market is evolving, companies would be well advised to build transfer pricing systems flexible enough to adapt to new industry norms. Further, companies will need to consider other non-transfer pricing aspects of taxation.

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