cell & gene

CELL & GENE THERAPY COMMERCIALIZATION CONSIDERATIONS

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GENE THERAPY: COMMERCIAL CHALLENGES AND STRATEGIC CHOICES

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Innovation in gene therapy brings the potential for transforming patient care and obviating the need for chronic therapy through single-dose cures. Despite the potential long-term benefits of this new therapeutic modality, gene therapy companies face a number of underappreciated challenges.

While there have been recent curative achievements in hepatitis C virus, curative small molecule or biologic therapies are uncommon. After three decades of hopes tempered by setbacks, gene therapy (the process of transferring exogenous protein-coding nucleic acids into cells to ameliorate a disease state through restoration or augmentation of host gene function) is poised to make curative1 therapies a routine approach for managing diseases.

Gene therapies, including both in vivo (i.e., intravenous administration of a viral vector carrying a gene for a missing or faulty protein) and ex vivo (i.e., genetic manipulation of harvested cells before administering them to the patient) approaches (see Figure 1), are starting to reach the market with pronounced, long-term impact after a single administration. The FDA recently approved Novartis' CAR T-cell therapy2, Kymriah, followed closely by Gilead's CAR T-cell therapy, Yescarta, for hematology oncology conditions. At the end of 2017, Spark Therapeutics' Luxturna, indicated for the treatment of an inherited form of vision loss, became the first in vivo gene therapy approved in the U.S. Further, gene therapy assets from AveXis for spinal muscular atrophy, BioMarin for he-

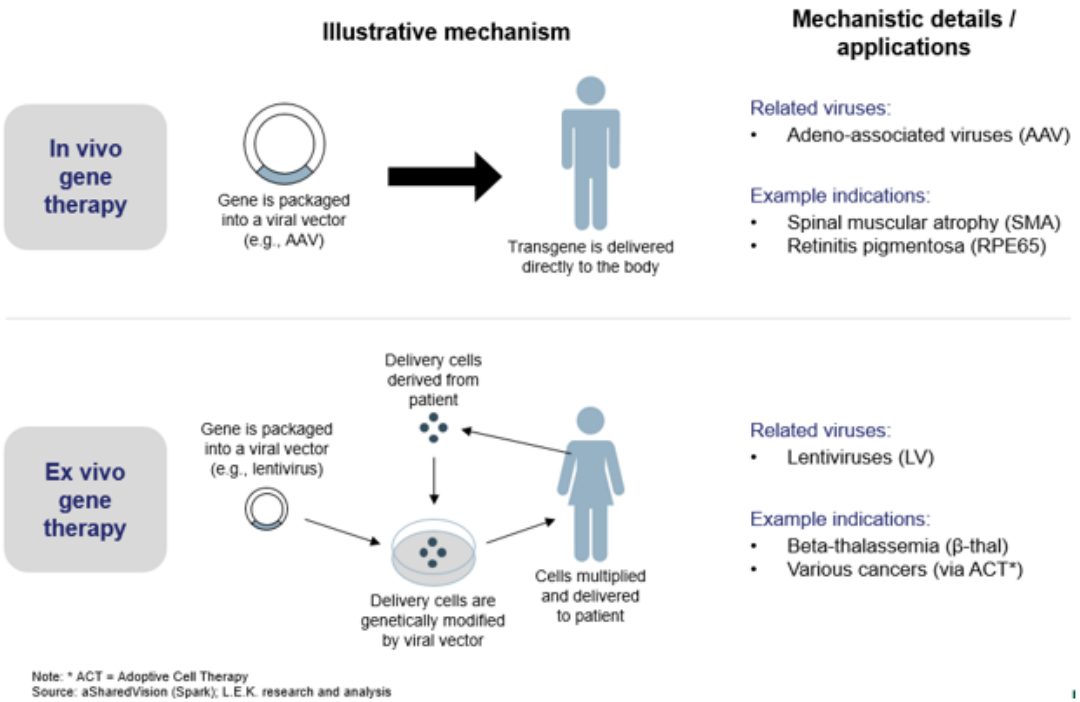

Figure 1: Overview of gene therapy modalities and related indications

mophilia A, and Nightstar for choroideremia, among others, have advanced to pivotal trials (or have been filed for approval) after demonstrating attractive earlier-stage data.

Building on these successes, large pharmaceutical companies are investing heavily in gene therapy (e.g., Pfizer's gene therapy deals with Bamboo and Sangamo, Novartis' acquisition of AveXis, and Roche's agreement to acquire Spark). Meanwhile, venture capital firms continue to fuel the creation of novel gene therapy platforms and approaches, leading to continued expansion of the gene therapy pipeline (see Figure 2).

This momentum, coupled with scientific, clinical, and manufacturing advances, suggests gene therapy will play an important role in managing diseases driven by specific genetic mutations. However, this new treatment paradigm will challenge biopharmaceutical companies to evolve their traditional business models to better serve patients, providers, and payers with this complex, novel therapeutic model.

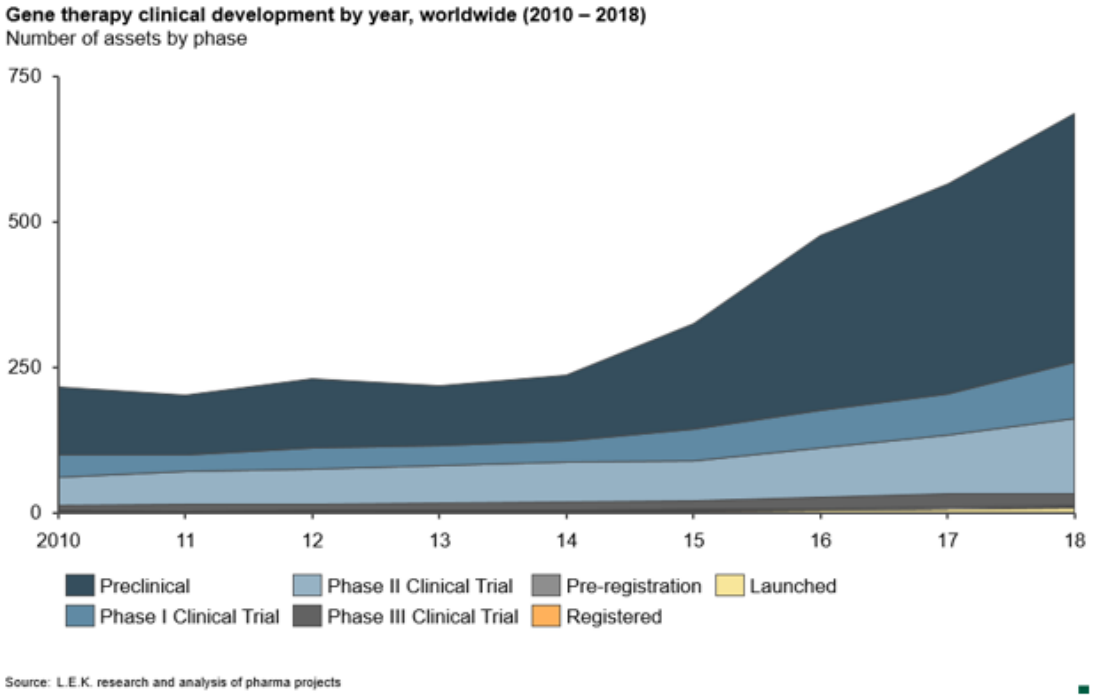

Figure 2: Gene therapy clinical pipeline evolution

GENE THERAPY COMMERCIAL CHALLENGES

The fundamental value proposition of gene therapy is long-term efficacy with a single-dose treatment. This novel treatment approach introduces a number of unique challenges for gene therapy companies.

1. Fast Depletion Of Addressable Populations

The achievement of a functional cure or the generation of antibodies against a delivery vehicle (e.g., a virus) is expected to limit gene therapies to a single dose per patient. An inability to re-treat would lead gene therapies to deplete their addressable prevalent populations (see Figure 3). As the number of treated patients accumulates, the number of potential patients who could be treated in a given year is reduced. This leads to

demand that peaks early before steadily declining. Once the prevalent population is depleted, demand for a gene therapy would be driven by incident patients.

While slow uptake of a gene therapy could make the demand "bolus" less pronounced, patient depletion would still inevitably occur, and incident populations would still drive long-term demand. This is mainly a challenge for conditions with addressable prevalent populations that are large relative to the incident population. Many diseases being targeted by gene therapy fit this description.

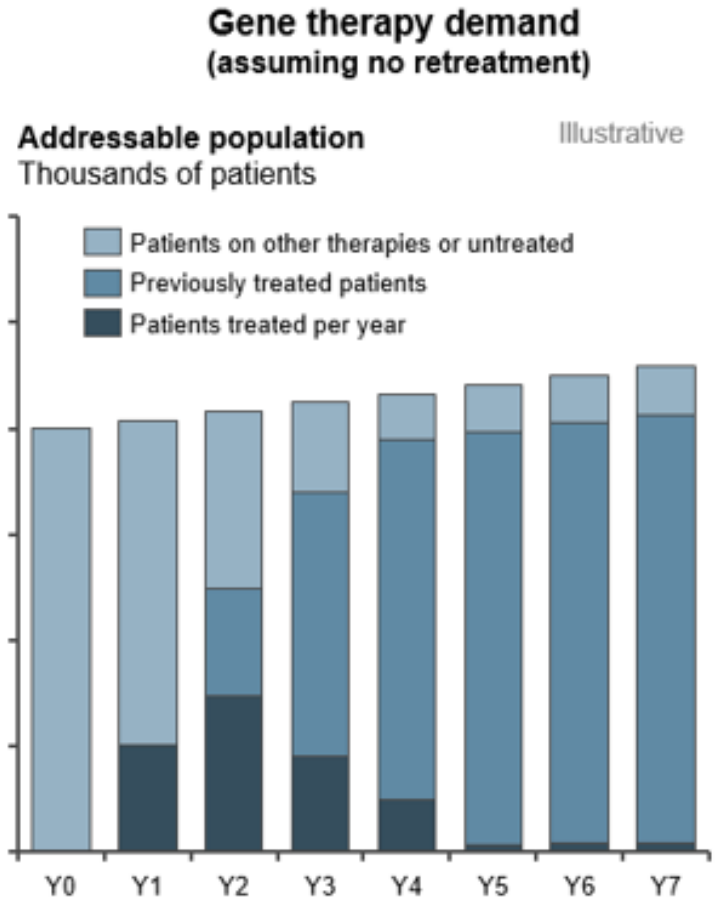

Figure 3: Gene therapy depletion of addressable patients

In contrast, therapies that focus on conditions driven by incident populations will likely have more stable long-term demand (in the absence of new market or competitive events), as the addressable patient population is renewed every year. Unfortunately, outside of oncology, the number of indications that are mainly driven by incident populations is relatively small, suggesting dynamics related to the depletion of addressable populations will be a hallmark issue for gene therapies.

2. Complex Market Access Dynamics

Price points for recently launched gene therapies have fallen short of expectations. For example, prior to the launch of Kymriah, industry participants projected a price of $600,000 to $750,000 per patient. However, the actual price of Kymriah at launch was $475,000 per acute lymphoblastic leukemia patient. Spark's Luxturna, which was able to achieve a relatively high price of $850,000 for the treatment of both eyes, fell short of the $1 million+ price point expected by the market.

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Payers are hesitant to pay high up-front costs for these therapies. This is partly due to the fact that curative therapies do not yet have a long-term track record of sustained efficacy. Under one-time payment models, there is a profound misalignment of short-term costs of gene therapy that would be borne by payers and long-term benefits accrued by patients. Payers are often hesitant to entertain one-time payments that are more than threefold to fivefold the cost of the existing standard of care. Furthermore, they are concerned with having to pay up front for a treatment that would provide benefits to a patient beyond his stay on their plan (typically less than five years).

3. Challenging Gene Therapy Franchise Sustainability

The "bolus-like" revenue curve associated with a first gene therapy presents a challenge to achieving sustainable growth given the lack of a stable base from which to build. Revenue will wane naturally as the addressable population is depleted a few years after launch. The short duration of meaningful revenue contributions from a single gene therapy product suggests the timing of life cycle management efforts and other product launches is critical.

Achieving growth would require launching another revenue stream (e.g., another gene therapy product) before the revenue of the first gene therapy starts to wane. This would lead to a situation in which the revenue peaks overlap, potentially resulting in substantial growth. However, maintaining growth would require launching a product every few

years. Beyond the question of whether a biotech company would have the portfolio breadth or resources to launch several products within a few years of each other, it would be challenging to optimally time the launches of subsequent gene therapies.

KEY STRATEGIC CHOICES FOR WINNING IN GENE THERAPY

As the gene therapy landscape continues to mature, biopharmaceutical companies need to make a number of strategic choices to drive success, given the commercial challenges articulated above.

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Global Head | L.E.K. Consulting

1. Mix Of Indications

As discussed, the nature of the addressable population for a given indication can have profound implications for the future demand for a gene therapy. Indications driven by incident populations are expected to lead to more-stable demand, while those driven by prevalent populations could see declining demand after an initial peak. Today, this mainly presents a choice between oncology and nononcology indications. Given the short survival spans for patients with advanced and metastatic cancer, the addressable population is driven by the annual incidents of patients. With the exception of a limited set of indications that are fatal a few years after diagnosis (e.g., spinal muscular atrophy type 1), nononcology indications tend to be driven by prevalent populations.

Within nononcology indications, gene therapy companies need to decide whether to pursue monogenic conditions, which tend to be rare, or broader conditions driven by a number of mutations or by unclear etiology. Given the technical considerations, gene therapy efforts are currently centered on monogenic conditions. However, novel platforms or competitive intensity could push gene therapy companies to consider diseases with bigger addressable populations despite higher technical hurdles.

There is no right answer on the appropriate mix of indications for a company to consider. However, it is critical to understand the potential downstream implications of pursuing different types of indications, as well as the existing and emerging competitive

environment. Ultimately, biotech companies should pursue indications for which they feel they have a competitive advantage relative to other players in the space.

2. Technology Risk Diversification

Most biotech companies focused on gene therapy are formed around a specific technology platform (e.g., novel viral capsid that could have preferential uptake in an organ system). Most then proceed to de-risk the technology as quickly as possible by applying it to low-hanging-fruit indications. However, the main common characteristic across selected indications is often the underlying technology platform that gave rise to the gene therapy candidates. This concentrates risk on the technology platform and exposes the company to a negative event that has a deleterious effect across the whole portfolio. Early-stage gene therapy companies often do not have a choice regarding this risk; however, once the founding technology begins to have traction, executives will often pursue adjacent or orthogonal platforms that diversify risk and maximize opportunities for the company.

Gene therapy companies may choose to develop different viral delivery vectors or technologies for ex vivo and in vivo applications. However, it is often difficult to know when to diversify away from the founding technology platform. Further, it is challenging to balance spend levels across founding and new platforms and to decide whether to develop new technologies in-house or access them from external sources. Importantly, strategic choices around technologies should dovetail with strategic choices about indication mix to ensure consistent direction for the future.

3. Leadership In Novel Reimbursement Models

Gene therapies represent a departure from the traditional biopharma business model. As reviewed above, they have the potential to introduce misalignments between long-term benefits to patients and short-term costs to payers. Resolving this misalignment is undoubtedly one of the greatest challenges facing gene therapy. While a number of industry efforts have begun (e.g., Alliance for Regenerative Medicine; discussion among Express Scripts, BioMarin, and Spark), it is unclear what the optimal gene therapy reimbursement model will be or whether individual models will emerge for specific indications, gene therapy situations, or geographies.

Regardless, gene therapy companies need to make a number of choices related to novel reimbursement models. First, do they want to pursue such models for their therapies? Second, how much of a leader do they want to be in the development of these business models? Third, when is the right time to engage the appropriate stakeholders? It is in the best interest of gene therapy companies to be engaged in relevant discussions as early as possible to ensure beneficial outcomes.

4. "Build Vs. Outsource" Operating Model

A number of leading gene therapy biotech companies have built out most, if not all, of their infrastructure. This is most evident in manufacturing, where companies such as BioMarin and AveXis have made significant investments in internal manufacturing capacity. These decisions were driven by a combination of the lack of external expertise and a desire to protect intellectual property and trade secrets. However, as we have seen before for small molecule therapies and antibodies, external manufacturing capacity will likely play a key role in supporting the gene therapy industry as contract development and manufacturing organization offerings mature. A number of players (e.g., Brammer [Thermo], Paragon [Catalent]) have started to invest significantly in this area. Ultimately, a combination of factors including portfolio breadth, uniqueness of the technology, and availability of quality external manufacturing supply will determine the optimal path for a given gene therapy company.

Further, given the potential impact of waning demand on the utilization of commercial and medical personnel, gene therapy companies may choose to outsource these capabilities. This dynamic has not yet started to play out and perhaps will be considered as more gene therapies start to reach the market.

SUMMARY

Technological advancements are making a way for gene therapies to deliver long-term benefits to patients with a single dose. This dynamic is expected to introduce a number of issues that will challenge the existing biopharma model, given short-lived demand curves and misalignments between short-term costs of gene therapy and long-term benefits to patients. Addressing the strategic choices behind these challenges will be critical for the sustainability of gene therapy business models.

4 STRATEGIES FOR SUCCESS IN THE CAR-T 2.0 MARKETPLACE

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& NAVAL SHANWARE
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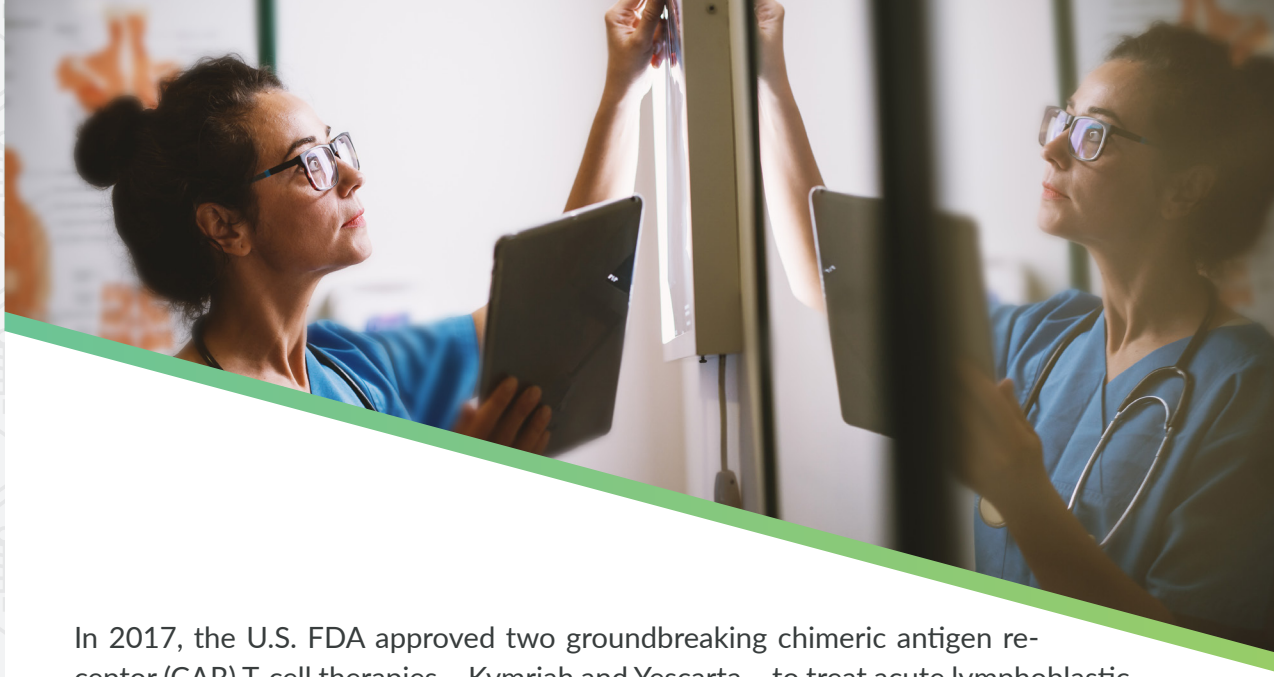

In 2017, the U.S. FDA approved two groundbreaking chimeric antigen receptor (CAR) T-cell therapies – Kymriah and Yescarta – to treat acute lymphoblastic leukemia and diffuse large B-cell lymphoma, respectively. These novel therapies utilize a patient's own immune cells to attack and kill the cancer, and they have shown promise in treating and, in a few cases, "curing" otherwise incurable hematological malignancies.

Despite the breakthrough nature of the clinical data, these first-wave CAR-T 1.0 therapies are struggling to find commercial success,[1] due to factors including:

- Logistic challenges with regard to patients successfully receiving the therapy in approved centers of excellence, and a waiting period of up to four weeks[2,3]
- Toxicity concerns with administering and receiving the therapy, frequently requiring hospitalization in intensive care
- Burdensome training and accreditation processes
- High cost of overall patient management, coupled with payment and reimbursement challenges
- Manufacturing production issues due to the complex nature of the therapy

Despite these commercial challenges, the clinical promise has helped trigger substantial follow-on research to harness CAR-T to treat other cancers, including multiple myeloma and solid tumors. In keeping with the tremendous excitement for these therapies, investment in a second wave of CAR-T drugs is strong, with more than 270 trials underway and exponential market growth estimated at nearly 50 percent between 2019 and 2028.[4]

POTENTIAL BARRIERS TO CAR-T 2.0 COMMERCIAL SUCCESS

As this second wave of CAR-T therapies begins coming to market in the next five years, their manufacturers will need to anticipate and prepare to address many of the same commercial challenges as their predecessors, as well as several additional ones, including:

- **Capacity constraints:** The next CAR-T approval is expected to be for the treatment of relapse and refractory multiple myeloma, a market with an annual incidence of 30,000 new cases every year in the United States alone.[5] Approval for multiple myeloma is likely to result in a substantial increase in requirements for CAR-T administration infrastructure, which, if left unaddressed, could provide a substantial drag on commercial performance.
- **Competition among manufacturers:** At present, it is unclear if one institute would offer CAR-T therapies from several competitors or if hospitals would have exclusive relationships with a single manufacturer. A preference for exclusivity would be a significant barrier to entry for the new players in the market.
- **Competition from other treatments:** Unlike CAR-T 1.0 therapies that were approved for patients with no effective treatment options, CAR-T 2.0 therapies are likely to have effective, branded competitors in the marketplace. For instance, in both multiple myeloma and chronic lymphocytic leukemia, several efficacious and off-the-shelf agents are already approved and readily available. In the absence of head-to-head data demonstrating superiority, CAR-T therapies — with all their attendant challenges — risk being reserved for late-line salvage use.
- **Competition for patients with community oncologists:** With multiple myeloma and chronic lymphocytic leukemia patients being effectively treated in the community, at present community providers are likely to compete for patient ownership. Lack of understanding and familiarity with the treatment, site of administration, and toxicity profile are key factors that could inhibit a widespread adoption of CAR-T therapy among community physicians.
- **More payer pushback:** Indications like multiple myeloma and chronic lymphocytic leukemia represent much larger patient populations with approved and effective targeted therapies, including some generic ones. As such, CAR-T 2.0 approvals may represent much larger budget impacts than CAR-T 1.0, and they could receive greater payer pushback due to potential restrictions on access and price pressures.

4 MARKET DEVELOPMENT STRATEGIES FOR CAR-T 2.0

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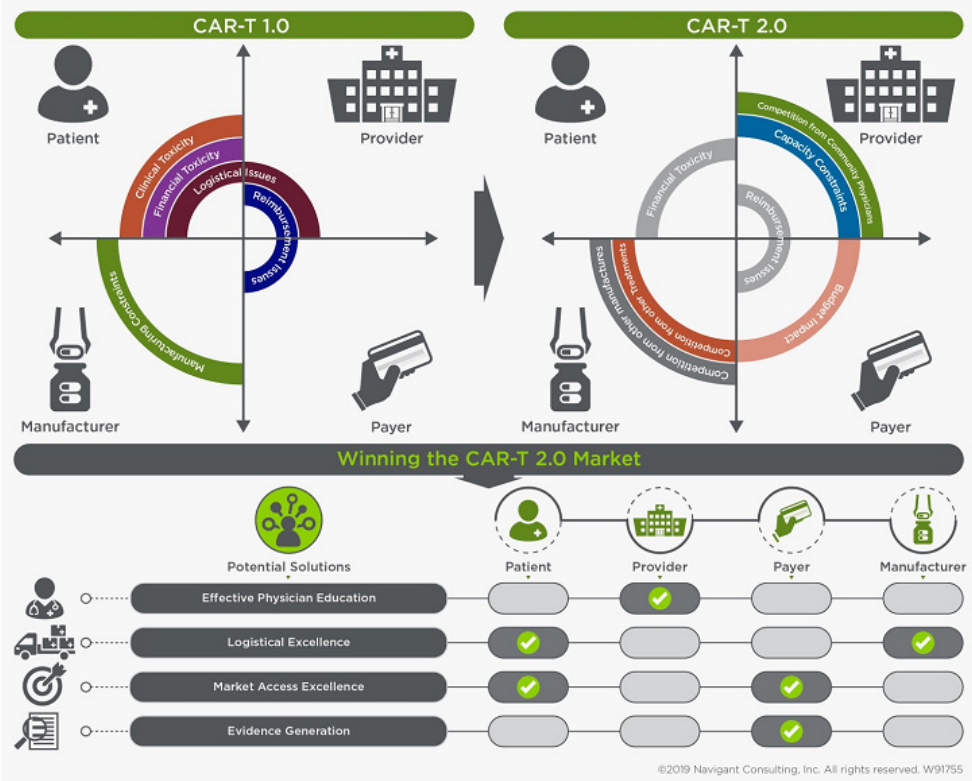
Innovators bringing the next generation of CAR-T therapies to market should give heed to and prepare to navigate the challenges identified above. Current and future players must recognize and execute against two key strategic imperatives: 1) optimizing the 360-degree stakeholder experience, and 2) demonstrating clear value through evidence generation. Preemptively addressing these likely future obstacles and opportunities early in the market development process will position CAR-T players well for CAR-T 2.0.

1. Effective Physician Education

To holistically optimize the stakeholder experience, 2.0 innovators must provide ef-



fective physician education. Currently, because of the novelty and complexity associated with CAR-T therapies, highly specialized medical experts at selected centers of excellence administer the vast majority of treatments. Indication expansion may lead to capacity issues at these centers, especially because these new indications generally are treated in the community.

One strategy to address these concerns is to facilitate CAR-T adoption in the community. However, to successfully drive adoption, it will be critical to effectively educate community physicians on CAR-T toxicity management, as well as on the clinical benefits of CAR-T therapies over other available options. Innovators that anticipate this shift and take measures to help community providers — who already treat nearly 55 percent of all U.S. patients — to adopt their therapies will gain a competitive advantage.[6] Players who fail to do so may risk being bypassed by these community providers in favor of other available agents. In other words, educating community oncologists will be a driving factor that determines the success of CAR-T 2.0.

While a wholesale move to the community may not be feasible in the near term, an initial shared ownership model is clearly possible. For example, consider this scenario: A center of excellence may require a patient to spend a week at the center to receive the infusion, as well as for immediate post-infusion monitoring, leaving the community physician to own other parts of the CAR-T patient journey. This shared ownership model could drive market success. In addition, this model could provide late entrants with a unique value proposition to differentiate themselves from early entrants that already have strong relationships in place with centers of excellence, for example.

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2. Logistical Excellence

With growing competition and a large addressable patient population, companies that can address logistical and manufacturing issues, with robust, simple supply chains, are expected to win in the CAR-T world. In fact, for the first time in the oncology marketplace, logistic strengths can be sources of sustainable competitive advantage. For example, while turnaround time of treatment options is traditionally a minor factor for

contemporary care providers, it likely will become a major one for CAR-T 2.0.

At present, manufacturing the CAR-T cells through reinfusion can take up to 30 days – that is a long time for a critically ill patient seeking treatment options to wait. In addition, first-wave manufacturers are experiencing product variabilities and capacity constraints. These issues are crippling CAR-T 1.0 adoption and already are giving advantage to innovators with better supply chains. Case in point: Novartis had difficulty manufacturing Kymriah due to unspecified product variabilities, which stalled its European Union launch, allowing competitor Gilead to be first to market.

Multiple CAR-T manufacturers are exploring manufacturing enhancements and alternative supply chain structures. Some of the approaches include increased automation and moving away from centralized to point-of-care manufacturing.

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If CAR-T 2.0 manufacturers do not address these manufacturing, production, and supply chain issues, they might find themselves left behind, as patients opt for conventional treatments dispensed in real time and competitors with robust systems in place gain preference.

In addition, CAR-T 2.0 manufacturers might find themselves left behind if they ignore the likelihood that hospitals will face disruptions to standard operating procedures across a number of factors, including patient selection, workup, scheduling, admission, care support, discharge planning, and follow up. Manufacturers that conduct provider impact analyses to help hospitals effectively onboard and scale procedures and best practices will have the advantage.

3. Market Access Excellence

Even if CAR-T 1.0 reimbursement and coverage issues are resolved in time for CAR-T 2.0, a host of other challenges looms large.[7]

First, there will be more competition within CAR-T 2.0 therapy, so 2.0 innovators will have to find a path to coverage and reimbursement and do so while positioning them-

selves against similar treatments and standards of care options. Manufacturers should prioritize payers as well as regulatory considerations when designing trials and focus on payer-relevant endpoints, such as overall survival in early-stage clinical trials. A properly planned trial with early inclusion of payer-relevant endpoints could eventually lead to mature and robust data by launch, making payers more comfortable covering these expensive therapies. Proactively addressing reimbursement issues, especially in the context of new "shared ownership" models, also will be critical to CAR-T 2.0 success.

Furthermore, as payers get actively involved in managing future CAR-T therapies, manufacturers should start thinking of innovative contracting options, such as performance-based payments, annuity payments, installment payment plans, or risk-sharing agreements to get payer coverage. Innovative payment methods in which cost is related to performance likely will be a way to win in the future.

4. Demonstrate Clear Value Through Evidence Generation

With the large price tag associated with CAR-T therapies and with advancements in conventional therapies, CAR-T therapies need to demonstrate a clear value proposition through the demonstration of clinical benefit over conventional therapies. In the absence of clear clinical benefit, providers will have little motivation to move from a familiar standard of care to a new, unfamiliar one.

For example, to date, initial objective response rate data for CAR-T treatment of relapsed and refractory multiple myeloma is compelling. However, durability of responses remains unknown, as follow-up data is limited.

Furthermore, even if CAR-T therapy for multiple myeloma is very effective, multiple conventional therapies with high success rates also are available. For example, recently daratumumab in combination with Velcade melphalan-prednisone (VMP) was approved for newly diagnosed multiple myeloma patients who are ineligible for autologous stem cell transplant (ASCT). The approval was based on a 90 percent objective response rate in the daratumumab arm compared to the control arm of VMP.[8] Now that an effective therapy for newly diagnosed multiple myeloma patients who are ineligible for regenerative ASCT exists, the entry bar for CAR-T therapies will rise for these patients, and endpoints that measure durability of response, such as progression-free survival and overall survival, will be emphasized.

For CAR-T 2.0 markets like multiple myeloma, head-to-head trials to evaluate and demonstrate clinical superiority over on-market therapies will be important validation. With the costs of frontline multiple myeloma triplets and quadruplets likely to be in the $300,000 to $500,000 range,[9] CAR-T therapies demonstrating improvements over the competition in earlier lines of therapies will help CAR-T 2.0 therapies gain preferential access.

WINNING THE CAR-T 2.0 MARKET

CAR-T 1.0 therapies entered a market that was unprepared for their novelty. CAR-T 2.0 innovators, being next in line, should take the opportunity to learn from the struggles of their novel predecessors, anticipate new and unique high-stakes challenges, and execute on a thoughtful strategy, to help fulfill the tremendous promise of these revolutionary therapies.

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RECALIBRATING THE SUPPLY CHAIN FOR ALLOGENEIC CELL THERAPIES

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In November 2018, I wrote an article about establishing a supply chain for autologous cell therapies — those formulated using a patient's own cells. This partner piece highlights considerations that need to be taken into account when developing a commercialization and supply chain strategy for allogeneic cell therapies, in which cells from a single donor are expanded and used to treat multiple patients.

As with autologous therapies, allogeneic products are normally developed to address the needs of a relatively small patient population, with very specific indications. Allogeneic therapies offer some obvious advantages from the production perspective. However, unlike autologous therapies — where the patient and their location are known from the outset — allogeneic therapies can be distributed to patients across a wide geographic area. In many cases, the point of care for a commercial allogeneic therapy is in a different location than the product's clinical trials sites. This presents challenges that are unique to allogeneic therapies, not the least of which is identifying where to position product inventory and distribution channels for delivery to an undefined network of caregivers.

In most cases, several CMOs and other partners contribute to the allogeneic production process, so at least the different links in the upstream supply chain are known. The challenge becomes understanding the storage and distribution environment necessary to deliver product to the patient — and what capabilities and distribution partners are

needed to ensure the safety and integrity of product across the chain of custody.

When developing a supply chain strategy and risk assessment plan, it is advisable to understand each of these entities and their roles and related responsibilities. As with all supply chains, the key is understanding the different participants, taking into account the locations, product/material profiles, and transportation options between these links in the chain.

DEVELOPING A BLUEPRINT FOR SUPPLY CHAIN MODELS

As always, a team approach is imperative. Include all participants (internal and external) in the definition of the overall process to include any activities and entities that contribute to — or could potentially impact — the seamless flow of material and product across the production life cycle.

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From a supply chain perspective, the production process is relatively simple, in many cases including a single site for the production of the drug substance. This, in turn, can be transformed into a drug product, filled into the unit of administration, packaged into primary and secondary pack components, and stored for distribution to market.

As with most biological products, there are temperature constraints. Temperature ranges to be maintained vary across the process steps, from acquisition of the initial starting materials, development of the master cell bank, production of the drug substance, formulation and filling of the drug product, final packaging, and distribution. Personal experience has confirmed these ranges can vary from ambient or controlled room temperature (CRT), cryogenic, frozen (at a variety of ranges), and 2 to 8 degrees Celsius. It is therefore important to define the end-to-end supply chain.

Defining activities, process steps, elapsed time, and product profile at rest and in transit provide the baseline. This should then be extended into best- and worst-case scenarios, highlighting risk factors that could negatively impact production, packaging, storage, distribution, and final delivery to the patient.

PRODUCT LIFE CYCLE MANAGEMENT CHALLENGES

For new compounds that are developed to meet the needs of a specific, very small patient population, in many cases the biggest challenge is predicting the demand cycle. Clinical trials provide an indication of the potential location for initial qualification and treatment of patients. However, as many of the patient treatment sites are related to the clinical trial partners, this does not provide the indicators needed to identify the steps along the patient journey, from diagnosis to remission. Many of these therapies require a weekly or biweekly infusion to be performed in a clinical location. This is a challenge for patients who are critically ill and need to travel to ensure ongoing treatment of their condition. Ideally, once their condition has improved the dosing regimen can be performed at a location closer to home — including local providers and clinics.

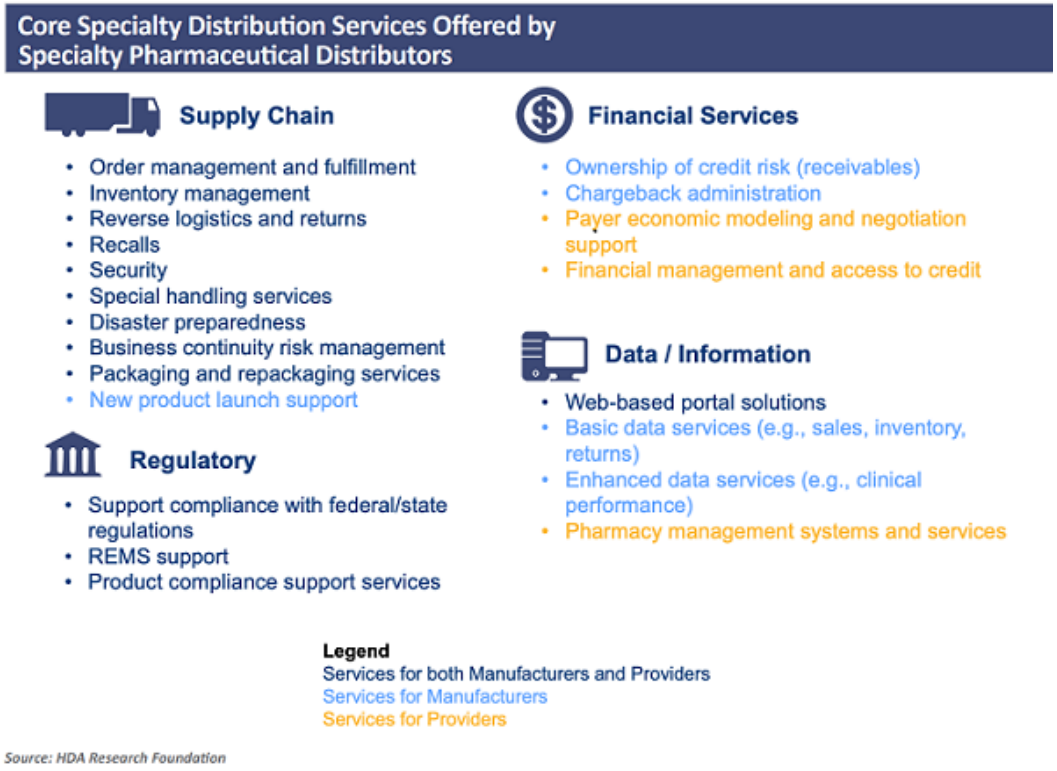
This presents its own challenges, not the least of which is identifying a potential patient population, geographic location of clinical studies, and treatment sites for delivery of the final drug product to the patient. Selecting appropriate partners for initial product introduction requires an understanding of the complexity of the patient journey and the product life cycle — in many cases these products have a relatively short shelf life. Strategies should include processes and procedures for the return and destruction of product, in compliance with the FDA, European Medicines Agency, and other regulators.

Another challenge from a storage and distribution perspective is that longer-term point of care requires the supply of the product to locations that can be geographically diverse. As such, the new product introduction strategy should take into account different transportation and delivery models, in many cases requiring several modes of transportation (road and air) as well as multiple handover points in the chain of custody. Supply chain planning should allow for different environmental hazards, integrating appropriate packaging, labelling, and time and temperature monitoring devices into the physical distribution model for each origin/destination pair.

Distribution is further complicated by the requirement in the U.S. for pharmaceutical distribution licenses for each state. When introducing a product to market, predicting geographic demand and applying for the appropriate licenses for each state can be costly and time-consuming. An alternative is to work with specialized third-party logistics companies that are licensed in all states and have the necessary infrastructure in place.

The overall supply chain strategy needs to take into consideration the initial launch stocks required to meet anticipated demand and to have a sufficiently flexible supply network to respond to variability in supply and demand. One strategy is to maintain the primary product inventory at a single global location. Variations in packaging configurations for different geographic regions can be addressed through postponement, performing the final packaging, labelling, and shipment to point of demand using just-in-time fulfillment models.

When faced with these challenges, most companies enlist the services of third-party logistics partners that have specialized capabilities. Services can include packaging, labelling, storage, repackaging, and final delivery to customers. In the U.S., the primary distribution channels include many different value-added services. This was well-defined in a report prepared by the HDA Research Foundation (https://www.hda.org/foundation). Figure 14 illustrates some of the specialty distribution services available.



Source: HDA Research Foundation

MAINTAINING THE DIGITAL DATA TRAIL

Unlike autologous therapies, where the vein-to-vein supply chain requires an audit trail for the specific chain of identity for unique patients, allogeneic therapies have the advantage that a single batch can be manufactured, stored, and distributed to meet the needs of multiple patients. Although it is still critical to ensure each step in the chain of custody is identified, monitored, and controlled, there are many advantages, not the least of which is the ability to maintain inventory in regional locations to meet the needs of a larger patient population. Collaborating with all participants in this chain of custody to share supply and demand data in near-real time provides the flexibility to balance fluctuations in supply and demand.

Obtaining a more detailed view of constraints and challenges across specific shipments, distribution channels, and activities provides a baseline for better planning and remediation in the event of a problem. The concept of the "control tower" is well-known in supply chain management. The detailed item- and shipment-level data that is captured provides a real-time and historical view across the shipment life cycle, a value that cannot be overestimated.

BENEFITS OF DIGITAL DATA — EXCEPTION MANAGEMENT AND REMEDIATION

Global regulations for the distribution of pharmaceutical products have been extended, and there are now requirements to provide a unique identifier — or serial number — at the single unit level for the majority of products. This requirement has been formalized in several regulations, including:

EU FALSIFIED MEDICINES DIRECTIVE

Enacted in 2013, this directive introduced track-and-trace regulations to monitor and control the safety and supply of medicines for human use. Requirements include:

- Serialization — manufacturers must mark packages with four data elements:
  - product identifier
  - serial number

- lot or batch number
- expiry date.

Serialization should take place at the secondary or salable unit to enable product verification across the chain of custody. By law, pharmacy dispensers must verify product identity prior to dispensing. Safety elements, including tamper-evident packaging and labels, must also be verified.

- Reporting — Reporting of product code, batch lot, expiry date, doses per pack, target market, and serialization detail must be done to the European Medicines Verification System to verify identity of pharmaceutical products for sale in the EU. In some cases, it is also necessary for supply chain partners to perform parallel reporting.

U.S. DRUG SUPPLY CHAIN SECURITY ACT (DSCSA)

The DSCSA is Title II of the Drug Quality and Security Act that came into force in 2013. The DSCSA defines the implementation model for an interoperable electronic system to authenticate and track marketed prescription drugs in the U.S. By 2023, this will enable serialized traceability for individual packages across the commercial supply chain.

In addition to these regulations, there are others in place and pending in areas across the globe. What they all have in common is increased oversight across the global chain of custody, with requirements to authenticate, monitor, and control the medicinal substances patients depend on. Although these regulations have increased costs for the packaging, labelling, and distribution of products, there are many benefits in addition to the obvious ones of ensuring the integrity of the product and patient safety.

As shipments move across the links in the extended supply chain, access to timely and accurate information becomes an enabler for process improvement and efficiency. For example, item- and product level-visibility — integrated into advanced receiving notifications (ASNs) — can facilitate the allocation of appropriate personnel and equipment needed to ensure that products do not experience delays on the receiving dock and can be placed in a secure storage location. Integrating these ASNs with warehouse management and other supply chain applications streamlines operational procedures and can

also provide alerts to ensure that the appropriate QA and other personnel are available at the time of delivery.

RECALIBRATING THE SUPPLY CHAIN

Conducting a risk assessment at different stages in the product life cycle is an obvious best practice. Having access to ongoing detailed information related to issues, constraints, and impact provides data that can be used as a framework for "what-if?" scenario planning. Understanding the likelihood and impact of changes across the product and shipment life cycle enables the adjustment of transportation planning, packaging, and other areas that impact the safe and secure delivery of product to patients. Using a risk assessment framework and communicating mitigation strategies across the supply chain network enables the flexibility and control needed.

Factors to consider in the risk assessment include:

- regulatory requirements — customs and border control as applicable
- trans-shipment points across the chain of custody
- changes in mode of transportation — potential environmental hazards
- weather hazards (differences in shipment and receipt locations)
- availability of receiving resources — personnel and material handling
- inspection and QA process — evaluation of excursion data from time and temperature loggers.

SUMMARY

Not all supply chains are equal — there is no one-size-fits-all mold. Taking into consideration the different physical characteristics of materials and products in the chain is only one aspect of developing an effective supply chain strategy. Developing a flexible model to support the demand profile of allogeneic products, with evolving patient populations, is imperative. The supply chain strategy needs to align with the overall patient journey. Follow these best practices:

- Evaluate the different configurations of networks and their relationship to the distribution models to successfully deliver each dose to point of care.
- Prepare for a variety of demographic and geographic differences as new prod-

ucts are introduced and adopted by the community of caregivers.

- Build a robust supply partner network to ensure variations in supply and demand will not impact the availability of product at “point of patient.”
- Understanding the differences between the traditional pharmaceutical supply chain models and those necessary to meet the complexity of allogeneic therapies is the first step on the road to successfully delivering on the promise of these amazing products.

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CAR T-CELL THERAPIES IN THE EU5: WHAT CAN WE EXPECT FROM PAYERS?

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In June 2018, in a landmark move toward advanced therapy medicinal products (ATMPs) — groundbreaking treatments based on genes, tissues, or cells — the European Medicines Agency (EMA) recommended the first two CAR T-cell therapies receive marketing authorization in Europe. Novartis' Kymriah (tisagenlecleucel-T) and Gilead's Yescarta (axicabtagene ciloleucel) secured approval from the European Commission (EC) in August 2018 for select aggressive hematological malignancies. Kymriah is indicated for relapsed or refractory diffuse large B-cell lymphoma (DLBCL) after two or more lines of systemic therapy, as well as pediatric and young adults (up to 25 years of age) with B-cell acute lymphoblastic leukemia (ALL) that is refractory, in relapse post-transplant, or in second or later relapse. Yescarta is also indicated for relapsed or refractory DLBCL and also for primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy.

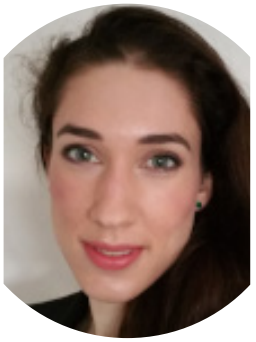
Notably, these innovative, personalized treatments are the first to be approved through the EMA's Priority Medicines (PRIME) program, which is designed to accelerate the approval of innovative drugs. The approved CAR T-cell therapies are patient-specific and produced by extracting a patient's own T cells (i.e., autologous). T cells are modified to express CARs that recognize a specific tumor antigen (e.g., CD19 in the case of Kymriah and Yescarta) before being infused back into the patient, where they proliferate and seek out and destroy the tumor cells (CD19-positive cells in the case of Kymriah and Yescarta). The first pioneering CAR T-cell therapies represent a paradigm shift in the treatment of cancer and a breakthrough for some relapsed or refractory hematological

malignancies, showing durable responses and potential for long-term disease control unrivaled by conventional therapy. However, there are weaknesses that are expected to hinder the widespread commercial uptake of the first CAR T-cell therapies. Not least, the hefty price tag of these one-time treatments will inevitably pose challenges for already budget-constrained national reimbursement authorities in Europe, and thus represents a potential barrier to ensuring widespread patient access and adoption.

The difficulty of balancing paying for innovation with budgets has plagued Europe for years, and the emergence of cell and gene therapies has only exacerbated that conundrum. The launch of the first two CAR T-cell therapies will likely prove to be useful case studies for how payers and physicians will respond to this new reality.

PAYER LANDSCAPE

In the U.S., Novartis has implemented indication-specific pricing for Kymriah: $475,000 for B-cell ALL and $373,000 for DLBCL. Yescarta's U.S. list price is $373,000 for DLBCL and PMBCL. In Europe, pricing strategies for Kymriah and Yescarta will be critical for securing optimal access and reimbursement from national authorities, and discussions are ongoing. At the time of EC approval, Novartis announced it "continues to collaborate with national health and reimbursement authorities across Europe on a fair, value-based pricing approach that is sustainable for national healthcare systems."



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Germany

When it comes to health technology assessment (HTA) and ultimately pricing and reimbursement, the approved CAR T-cells will benefit from their orphan drug status, as the EU5 countries (France, Germany, Italy, Spain and the U.K.) have formal or informal processes in place that allow for more lenient appraisals of orphan drugs. In particular, this is crucial for success in countries that are typically quite rigid about clinical trial design, such as Germany (where overall survival is the only acceptable efficacy end point for oncology therapies and single-arm trials are heavily frowned upon).

Although all drugs in Germany are reimbursed once they are approved by the EMA, not

all drugs are guaranteed a good price. This is determined by the added benefit rating, as assessed by the Institute for Quality and Efficiency in Healthcare and the Federal Joint Committee (G-BA). Orphan drugs are guaranteed a positive added benefit rating under the German HTA system, meaning they will not be reference-priced and do not have to submit full HTA dossiers. However, because HTA and final price negotiations do not happen until after a drug has been available for 12 months, we do not currently know how Germany will assess the CAR T-cells. Initially, Novartis has set a price of 320,000 euros (approximately $371,000), although that is presumably under negotiation with the sickness funds that will pay for the treatment.

One thing we do know, however, is that German payers anticipated the arrival of these high-cost agents. In January 2018, in response to the emergence of cell and gene therapies and their high price tags, the G-BA removed a previously little-used exemption from its HTA system, where drugs whose use would be limited strictly to the hospital setting did not have to undergo a benefit assessment. How do we know this was because of cell and gene therapies? The G-BA mentioned it right in the press release. In November 2018, Decision Resources Group (DRG) interviewed payers across the EU5 on the emerging market access landscape for Yescarta and Kymriah in DLBCL, and it became clear that removing the hospital-only exemption was not the only change anticipated in Germany.

Germany is a country that traditionally shies away from complex managed entry agreements (MEAs) or other forms of discounts, yet interviewed German payers indicated the high prices and high levels of uncertainty that come with Kymriah and Yescarta meant not only were they considering outcomes-based agreements, but they were actively pushing for them.

"We are highly interested in contracts regarding paying in installments and paying for performance, and that is something that Novartis and Gilead are not really interested in, but a lot of other companies are. We think it makes sense that we only pay a handling fee to the hospital, and say okay, that's enough for the CAR T-cell therapy and the hospital is getting 2,000 euros and the rest is something we have to negotiate between Novartis and ourselves. And I say to the company, we will pay not at once, we will pay it over five years and if specific metrics are not met after three years because they were not really cured, then we will stop paying. So this is something we are thinking about, and we discuss with the politicians." — Krankenkassen member, Germany

United Kingdom

German payers were not the only ones to anticipate the need for monitoring the efficacy and outcomes of these therapies, with the National Institute for Care and Health Excellence (NICE) in the U.K. already coming to a similar conclusion by relegating the drugs to the Cancer Drugs Fund (CDF), where they will have a set amount of time to prove their efficacy through collected real-word data before being re-reviewed for baseline commissioning for the National Health Service (NHS).

Yulia Privolnev

Manager, Global Market Access Insights | Decision Resources Group

NICE and the NHS were hailed by the industry for the quick acceptance of CAR T-cell therapy when they published draft guidance in September 2018 announcing the NHS would fund Kymriah for the treatment of ALL via entry into the CDF, despite its list price of 288,000 pounds ($366,000), considered to be the fastest funding approval in NICE history. This expediency was likely in part due to preparedness on the part of U.K. payers, who completed a mock assessment prior to approval that demonstrated the drugs would likely be cost-effective, at least in some populations. As a result of that mock assessment, the NHS began to build a network of specialist clinics in preparation for actual approval, meaning patient access would not be hampered once the drugs were properly approved. It should be noted that both Yescarta and Kymriah were rejected in draft guidance for the treatment of DLBCL (in August and September 2018, respectively) owing to lack of comparative data against salvage chemotherapy. However, in November 2018, Yescarta beat Kymriah to become the first CAR T-cell therapy to secure a positive recommendation in final guidance from NICE for DLBCL (and PMBCL). Yescarta was approved as a result of a confidential discount; it would have cost nearly 300,000 pounds ($387,000) per patient at its full list price, but Gilead's commercial agreement with the NHS enabled NICE to approve its entry into the CDF.

Notably, in January 2019, the Voluntary Pricing and Access Scheme replaced the Pharmaceutical Pricing Regulation Scheme (the backbone of how drugs are priced in the U.K.), and one key tenant of the new scheme was a promise for earlier engagement to ensure NHS physicians and NHS infrastructure are ready to accommodate and use new technologies arriving on the market, particularly cell and gene therapies.

U.K. payers interviewed by DRG were concerned about the trial design of the CAR T-cell therapies, specifically the lack of data comparing the therapies to chemotherapy, and their ability to demonstrate cost-effectiveness. They were ultimately proven correct with the initial rejections due to lack of cost-effectiveness. However, the introduction of MEAs through the CDF meant the therapies could be recommended for use, despite the costly monitoring required.

"You have to deal with three issues: cost-effectiveness, affordability, and uncertainty. So, the cost-effectiveness story … If you're saying you can cure ALL relapse, say give 10 years, you can put a list price of half a million, $250,000 to be effective over five years. Affordability is this 20-million-per-item in any three years, that's the budget impact test. But for these compounds and these indications, we're going to blast that out of the water. So, what's going to happen is the budget impact of 20 million per year is going to be breached. So, we've got to go back to the drawing board on price. The final bit is uncertainty. Now, if you look at, for example, Kymriah. There was significant uncertainty in their model. Kymriah failed, I think, on three things. The first is the single-arm study had no comparative data to standard of care. And, so, there were arguments around survival and standard of care. … We have to resolve that before we can move forward." — NICE advisor, U.K.

France

In France, Kymriah and Yescarta have been available for prescription through the early access program known as the l'Autorisation Temporaire d'Utilisation (ATU) since July 2018 for all eligible ALL and DLBCL patients (not just on a named-patient basis). The ATU program is important for gathering real-world data that can be used during pricing negotiations, as well as for winning over key stakeholders and uptake among key opinion leaders. French payers interviewed by DRG acknowledged the difficulties in terms of infrastructure and logistics associated with the manufacture of Kymriah and Yescarta, but were adamant they would be reimbursed and qualify for the highest possible improvement in actual benefit rating (Amélioration du service médical rendu [ASMR]), an ASMR I, meaning they show important added benefit over currently available treatments and would thus qualify for a premium price. However, a high ASMR rating also means these treatments must present pharmacoeconomic data to payers, a relatively rare occurrence in the French system.

"I think that the results are very important. But don't forget that these therapies require specific units, specific infrastructure and installations, and specific personnel. We also need to determine the daily pricing for this technique and to ensure that all will follow this price, but, once this is all done, these therapies will be used. I think they will get an ASMR I." — HAS advisor, France

Italy

The reaction of payers in Italy has so far been less transparent, as the drugs are still undergoing pricing and reimbursement negotiations. However, interviewed payers believed Kymriah and Yescarta would be reimbursed and awarded innovative status. In Italy, this means exemptions from certain payback schemes and instant inclusion on all formularies. Italy has historically used outcomes-based agreements to fund high-cost therapies, particularly for oncology therapies, and it is likely such schemes will be used for the CAR T-cell therapies.

"Obviously, the payers are terrorized by the idea of paying for CAR T-cell therapies — terrorized how to limit their use and to be sure that the prescription is appropriate. I think that the CAR T-cell therapies, as well as other high-cost therapies, will be limited, strongly limited, to some specialists, for instance, in this case oncologists and only to high-ranked hospitals, not to all of the hospitals. In Italy, there are a number of different hospitals. Usually the only ones that are enabled to prescribe expensive drugs are the university hospitals." — PTOR member, Italy

Spain

In a surprisingly quick approval, the Spanish healthcare system approved the reimbursement of Kymriah in December 2018. Notably, national payers, working with the regions, agreed on an outcomes-based agreement for ALL and DLBCL that will result in a price that is sustainable for the national health system. It was also announced that a similar agreement was being negotiated with Gilead for Yescarta for its approved indications.

"I think the CAR T-cell therapies at the beginning will be restricted to a small number of patients, and later some more patients will start to use them. But at the beginning its use will be restricted for reasons of cost-containment, and secondly because there are a lot of uncertainties about clinical outcomes for these patients. Payers at different levels will require more clinical data for these therapies to be used widely." — DGFPS advisor, Spain

WILL PHYSICIANS BE FREE TO PRESCRIBE CAR T-CELL THERAPIES?

In October 2018, DRG surveyed 250 hematological oncologists across the EU5 on their anticipated use of CAR T-cell therapies in DLBCL (the indication both Yescarta and Kymriah are labeled for) and what barriers to prescribing they anticipate. Unsurprisingly, most surveyed physicians agreed or strongly agreed the CAR T-cell therapies will fulfill an important unmet need for relapsed and refractory DLBCL treatment and that they

have the potential to replace allogeneic stem cell transplantation in select patients.

Despite heralding a paradigm shift in treatment for select patients, physicians anticipate multiple factors will limit the uptake of Kymriah and Yescarta for DLBCL, owing to clinical, access, and reimbursement hurdles. Approximately half of surveyed physicians across the EU5 (47 to 59 percent) expect the budgetary impact of these therapies to be the main factor limiting their prescribing. Also, a smaller percentage of physicians acknowledge the national-level payer restrictions (27 to 50 percent), along with the regional/local/hospital/clinical restrictions (30 to 35 percent), will likely limit the uptake of these therapies.

Aside from the frequent factors limiting prescribing/uptake, approximately a quarter of surveyed physicians across the EU5 reported the limited number of specialized units/centers for treatment (38 to 55 percent), the lack of experience/familiarity (24 to 47 percent), and safety and tolerability concerns (30 to 54 percent) will also limit uptake of Kymriah and Yescarta for DLBCL.

Like the interviewed payers noted, it's clear from the physicians surveyed that the specialized units/centers required will be a big factor in determining the uptake of the CAR T-cell therapies. Payers in the U.K. have been proactive about such a hindrance, but it's not clear all EU5 payers have.

CONCLUSION

The recent approval of the first CAR T-cell therapies in the EU5 has been quite a promising sign for other emerging cell and gene therapies, proving payers can stomach a hefty price tag when the drug's efficacy warrants it. Despite concerns about uncertainty in the data, payers have embraced CAR T-cells and physicians anticipate prescribing them to a cohort of their patients. However, CAR T-cells have also demonstrated the importance of preparation and engagement with relevant stakeholders as early as possible, as seen in the U.K., because healthcare systems are not necessarily prepared for the logistical challenges presented by these innovative therapies. Furthermore, as was seen in the U.K. and Spain, and will likely be seen in Italy and Germany, the likelihood that these types of therapies will have to be accompanied by MEAs, specifically outcomes-based ones, is quite high. These agreements allow payers to better balance paying for innovation and their budgets and for manufacturers confident in their products to achieve a higher price when the drug works. If Kymriah and Yescarta are anything to go by, the future looks bright for ATMPs in Europe.

4 EMERGING COMMERCIALIZATION STRATEGIES FOR GENE AND CELL THERAPIES

WALTER COLASANTE, PASCALE DIESEL & LEV GERLOVIN
CRA

Progress in development of gene and cell therapies around the world has potential to transform standards of care for a range of diseases and address significant areas of unmet need in healthcare over the coming years. In the U.S. alone, almost 20 gene and cell therapy products have been approved thus far,[1] with many other development programs reaching later clinical stages. The technology platforms of many of these drugs also offer the potential for curative efficacy and expansion for use in multiple indications.

Along with significant promise, gene and cell therapies also present a range of characteristics that can increase risk and cost, and thereby limit prospects for sustainable commercial success. Factors including complex and lengthy manufacturing requirements, very small patient populations, and short duration of treatment with curative outcomes that will reduce the pool of appropriate patients for treatment can have a significant impact on commercialization strategies. Many new drugs also lack evidence of durable long-term efficacy and safety, generating concerns among stakeholders, including regulators, clinicians, patients, payers, and industry partners. Examples of gene and cell therapies launched thus far indicate that commercial success can be a challenge even in cases where drug developers win regulatory approval. Among 10 novel gene and cell therapies approved in Europe since 2009, only six are still commercially available today.[2] The remaining four (ChondroCelect, MACI, Provenge, and Glybera)

were all withdrawn from European markets due to failed commercialization efforts.[2] Recently, our team at CRA conducted an analysis of the challenges associated with go-to-market models for gene and cell therapies. This review strongly indicates that traditional commercial and marketing strategies may not be directly transferable for maximizing chances of success for many of these new drugs. Companies advancing these clinical development programs will need to consider new or significantly modified commercialization models while also embracing advanced technologies to maximize efficiency and continually meet production requirements.

UNDERSTANDING THE COMMERCIAL CHALLENGES

Fundamental challenges in commercialization include costs and limitations in production methods. In just one example, producing autologous therapies such as chimeric antigen receptor T (CAR T) cells or stem cell therapies requires a process that must be replicated in individualized batches, which can present challenges in efforts to scale up production to meet global demand. The administration of these therapies can also present complications. For autologous treatments, a sample is taken from the patient, sent away for processing and modification (often to a single location regardless of geographic origin), and then dispatched back to a designated treatment center for re-administration to the patient. This process requires strict controls and quality standards, including traceability and a robust and reliable chain of temperature control. Planning for this process can mean considerable procedural and regulatory hurdles related to licensing, monitoring, and troubleshooting.

In addition to raising concerns among clinicians and patients, the lack of robust and conclusive long-term safety and efficacy data for many gene and cell therapies also presents challenges to regulators. When a U.S. Food and Drug Administration Advisory Committee unanimously recommended approval of Spark Therapeutics' Luxturna for treatment of inherited retinal disease in October 2017,[3] they cautioned that a lack of long-term follow-up data makes it unclear whether efficacy could diminish over time. They also raised questions about the potential for future adverse events not demonstrated in clinical research.[4]

Walter Colasante
CRA's Life Sciences Practice

Limitations on data can also fuel the perception that some gene and cell therapies do not provide significantly increased clinical value over existing therapies, making it difficult to justify often-high prices. To address any limitations on available data, regulators and payers often require companies to establish and maintain cumbersome and costly programs in patient monitoring and real-world data capture and reporting.

Pascale Diesel
CRA's Life Sciences Practice

Companies working to commercialize gene and cell therapies may also face challenges in identifying and effectively targeting stakeholders. In many traditional models, marketing and advertising budgets and large sales operations can be leveraged to communicate the benefits of therapies to clinicians, healthcare providers, and patients. But this conventional approach is often not suited to gene and cell therapies, which may require a more tailored marketing strategy to effectively target very small patient populations with distinctive characteristics. Drug developers may evolve their conventional models to new channels and new content to meet the unique needs and stakeholder populations associated with gene and cell therapies in the years ahead.

EMERGING STRATEGIES TO SUPPORT COMMERCIALIZATION

Drug developers are working to identify and implement a range of adaptive commercialization strategies that address these and other challenges while simultaneously embracing the distinct advantages that gene and cell therapies can offer.

1. Fast And Flexible Manufacturing And Supply Chain

Shorter duration of treatment associated with some gene and cell therapies can mean that both production and pricing models based on longer-term or lifetime dosing may not be applicable or adaptable. Pricing will need to reflect the fact that duration of treatment may be a matter of days or weeks versus years, more in line with medical innovations than with traditional drugs. In addition, approval of a potentially curative therapy may require a rapid spike in production that is not sustained over the long term. Both factors may require previously unnecessary levels of flexibility in production and distribution. Many industry insiders expect that, as gene and cell therapy development

programs progress, there will be greater demand for advanced innovative production and distribution technologies, including, among others, advanced cryopreservation tools and services. Companies will need to identify engineers and other skilled technicians with the ability to identify and operate the technologies necessary to support production goals. They will also need to plan for intensive and potentially short-term changes in production capacity early in the product life cycle.

2. More Precise Patient Targeting

To facilitate commercial success, it will be necessary for companies to support clinician efforts to screen and identify appropriate patients quickly at all stages, from clinical development through commercialization. Widespread, continuous, and precise biomarkers and related diagnostics will become essential tools.[5] Predictive analytics will also be important to define appropriate patient cohorts and then use that information to design and implement effective marketing and access plans. Claims data analyses of diagnoses and procedures at the local level will have to provide invaluable input when mapping the patient journey and designing a marketing and commercial strategy to be in sync with the patient experience. To support commercialization goals, manufacturers should also consider using predictive analytics to inform strategic decisions on the appropriate number of treatment sites, where they should be located, and whether and how they could facilitate delivery of gene and cell therapies directly to patients.

3. Collaborating With The Right Stakeholders

Many manufacturers of gene and cell therapies are also now turning to multidisciplinary stakeholders, including healthcare providers (HCPs), patient advocacy groups, patients, and clinicians, who can provide important perspectives and demands related to market adoption and commercial strategies. They turn to patient advocates to build precise assessments of the benefits and burdens of different drug delivery methods and, in some cases, to assess treatment protocols and dosing options and even some issues related to distribution, treatment site location, and longer-term patient monitoring. Stakeholders can also

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offer insights that can impact market access after product launch and support decisions related to pricing. In one example, the Duke-Margolis Center for Health Policy consortium in Washington, D.C. was created to bring together gene therapy manufacturers, payers, patient advocates, HCPs, and regulatory and policy experts to explore the feasibility of innovative payment models,[6] which industry is quickly realizing may be necessary to support reimbursement of many gene and cell therapies. To maximize the benefit of these collaborations, gene and cell therapy companies now often reach out to a broad range of stakeholders early in the drug development process and maintain active engagement throughout the planning and execution phases of commercialization efforts.

4. Seeking New Opportunities For Growth

To increase the chances of commercial success, companies developing gene and cell therapies should work to identify and pursue opportunities for growth where possible. Many experts agree that these drug developers should focus initial commercial efforts on the U.S. and EU and then expand to other geographic areas once they establish best practices, recognizing that this approach will depend on the global prevalence of a target disease. However, in some cases, gene and cell therapy companies might also target less developed markets where new curative therapies can be rapidly positioned as standard of care without the need to first consider incremental advances in treatment or symptom management.

Some gene and cell therapies present a diversified development platform with a unifying focus that can create additional commercial opportunities. Companies should consider adopting technologies and production processes that can be adapted for use in different therapeutic areas in the future. They might also conduct research initiatives to better understand genetic factors associated with many diseases, following the models used in the Human Genome Project and the International HapMap Project. This type of research can lead to more gene and cell therapies, with the potential to expand treatment to additional indications, potentially including disease states with large patient populations.

CONCLUSION

While some new best practices to support gene and cell therapies are already in place

or emerging, many companies working to develop these therapies will need to rethink the structure of their go-to-market models. Innovative, high-value processes and technologies that focus on speed, precision, and customization will be essential competitive advantages. Many companies will also need to consider collaboration with and support from a wide range of stakeholders, including patient advocates, HCPs, and payers. Successful commercial planning will also require companies to identify and plan for the full range of commercial opportunities for their technology platforms. With these new approaches, industry has the potential to optimize both patient access and commercial opportunities associated with the new generation of promising gene and cell therapies, many of which will be available to patients in the near future.

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SPARK'S LUXTURNA GENE THERAPY: WHAT CAN WE LEARN FROM ITS DEVELOPMENT & COMMERCIALIZATION?

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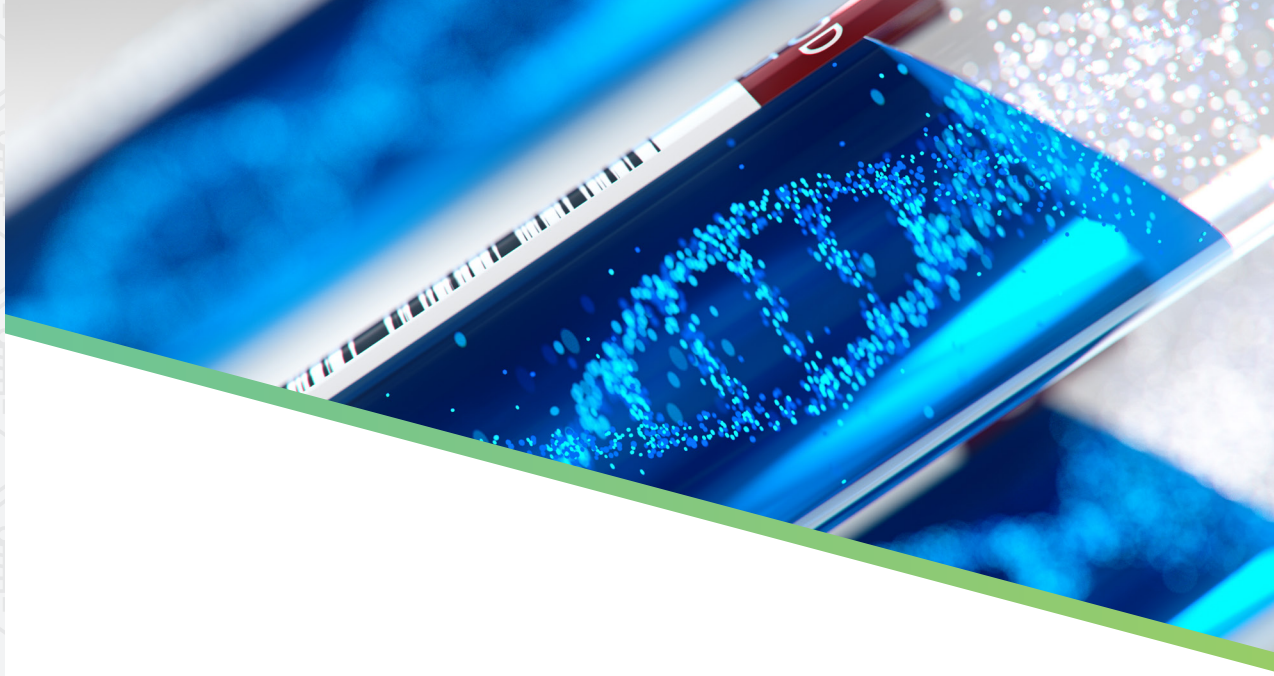

In Part 1 of this two-part article, we introduced, at a high level, the burgeoning gene therapy pipeline, and we covered key clinical development challenges facing companies in this arena. Here, we review lessons from Spark Therapeutics' pivotal program for Luxturna, a gene therapy approved for the treatment of patients with retinal dystrophy associated with confirmed biallelic mutation in the RPE65 gene, and summarize key considerations for the clinical development and commercialization of gene therapies.

LESSONS FROM THE CLINICAL DEVELOPMENT OF SPARK THERAPEUTICS' LUXTURNA

Luxturna's pivotal clinical program highlights several successful solutions to key clinical development challenges facing gene therapy developers working on monogenic rare diseases. To bring the agent to market, Spark and academic collaborators developed and validated a novel outcome metric measuring functional vision and conducted a study to collect natural history data in Luxturna's target patient population, and the company included control patients in the small, open-label Phase 3 study.

The multi-luminescence mobility test (MLMT) evaluates the ability of a subject to navigate an obstacle course at varying light levels. The end point was validated in a one-year prospective trial conducted with 26 enrollees with normal vision and 28 participants di-

agnosed with an inherited retinal dystrophy. The MLMT reliably distinguished between subjects with normal vision and those with vision impairment, and was able to measure decline in visual function in patients across repeat visits over the course one year.[1] Although interviewed ophthalmologists and payers generally hold a positive perception of Luxturna's efficacy based on the MLMT data, the impact of treatment on real-world activities of daily living remains uncertain (e.g., ability to read, work).

To supplement their data package and contextualize the treatment benefit conferred by Luxturna, Spark also conducted a retrospective chart review of 70 patients in Luxturna's target population — patients with confirmed biallelic RPE65 mutations. The data highlights the sizable and progressive decline in visual acuity and visual field size as a function of age, with the threshold for legal blindness generally crossed by age 20.[2]

Importantly, the pivotal Phase 3 trial for Luxturna, although small in size, included a control arm to establish the statistical significance of the agent's impact on the MLMT primary end point. After one year, the nine control patients were able to cross over into the active treatment arm. According to Spark, the pstudy was the first successful Phase 3 randomized controlled trial of a gene therapy.[3]

COMMERCIALIZATION AND MARKET ACCESS CHALLENGES FOR GENE THERAPIES IN RARE DISEASES

As incentive to invest in the development of an innovative gene therapy for a small rare disease population, marketers desire and seek a high price point. But, they must present a compelling case for the value of their novel medication and must operate within the confines of payer budgets. Numerous factors can influence the value discussion for a gene therapy, including the durability of the treatment effect and the reduction in medical costs associated with the management of the disease in question. Furthermore, although many monogenic rare diseases have a pediatric onset and may confer a tremendous burden on parents and caregivers — financial and otherwise — these indirect costs are not normally absorbed by payers, and their integration into the value discussion remains a topic of debate.

In our research, U.S. payers stress two key factors influencing the decision to reimburse a gene therapy: budget impact and cost-effectiveness. Budget impact is usually determined at the plan level; a payer's goal is to estimate how the added expense of

reimbursing the gene therapy will impact their members' premiums for the following year. Although cost-offsets may be realized as a result of a decrease in medical expenses that accompany the use of the gene therapy, some U.S. payers contend such offsets are most compelling when realized within the same year they incur the cost of the gene therapy. In single-payer systems (e.g., national health authorities in European markets), where organizations are responsible for the health coverage of a patient over the long-term, interviewed payers reported cost-offsets play a larger role, as cost savings can more comfortably be integrated over time.

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The key goal of a cost-effectiveness analysis is to ensure novel therapies deliver utility — the total benefit patients gain from therapy, often measured in quality-adjusted life-years (QALYs) — commensurate with their price, which should meet a market-specific cost per QALY threshold. These evaluations are challenging to conduct, even in non-rare diseases, and payers may rely on assessments from a third party such as the Boston-based Institute for Clinical and Economic Review (ICER) in the U.S. and the National Institute for Health and Care Excellence (NICE) in the United Kingdom. In ultra-rare diseases, the discussion around the fairest means to assess value continues to evolve.

LESSONS FROM THE VALUE DISCUSSION AROUND LUXTURNA

Luxturna launched in the U.S. at a cost of $850,000 ($425,000 per eye)—below the expectations of some analysts but in excess of the price necessary to meet standard cost-effectiveness thresholds ($100,000 to $150,000/QALY) in most iterations of an ICER analysis.[4]

ICER's review of Luxturna underscored the key data gaps that may impact cost-effectiveness analyses of a trailblazing gene therapy. For instance, although the clinical trials featured MLMT as the primary outcome metric, the same is not true for ICER's cost-effectiveness analysis. Owing to the novelty of the MLMT metric, there was no available data to correlate the MLMT results with the benefit/utility patients are expected to derive from the therapy. As a result, visual acuity and visual field, on which Luxturna de-

livered more modest clinical gains, had to be used in place of MLMT. Furthermore, the utility curve used to correlate visual acuity with a given utility was derived, of necessity, using data based on other patient populations, owing to the lack of data specifically in Luxturna's target patient population.

One key unanswered question in the analysis relates to onset of treatment; owing to the progressive nature of the disease, younger patients (i.e., age 3) would gain a larger health benefit and, thus, support a higher price point for Luxturna. However, it is unclear if patients could be reliably diagnosed as toddlers, especially considering that a segment of patients presents with late onset. As such, payers may be unwilling to accept the analysis assuming treatment at age 3.

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The durability of treatment benefit was another point of contention in the evaluation of Luxturna's cost-effectiveness; Spark has follow-up data from a Phase 1 trial supporting an efficacy duration of four years but believes Luxturna's benefits could persist much longer, possibly over a lifetime. However, ICER's health economists rely only on published data and therefore assumed a duration of 10 years, followed by another 10 years of progressive loss of function. Only time will tell whether the durability assumption used in the analysis reflects reality.

KEY CONSIDERATIONS FOR DEVELOPERS

More than 100 gene therapy programs are now advancing in the pipeline, and more than half of these programs have yet to establish clinical proof-of-concept. As developers chart a course to market for their innovative medications, key decisions are necessary across the product life cycle.

Target disease: If the target population size does not enable recruitment of enough patients for a control arm or a robust statistical analysis, take steps to collect natural history data in line with FDA recommendations. Developers should also consider features such as accessibility of target tissue and the need for systemic administration. The burden of proof for the safety of systemically-administered gene therapies may require

a more extensive safety characterization in the preclinical or early-clinical stages of development.

Trial design: Data from pivotal clinical trials of a gene therapy ideally secures buy-in from regulators, payers, and treating physicians. If a novel end point is necessary, get input from key stakeholders as early as possible and design a study to validate the new metric appropriately. When the efficacy gains expected in a trial are more modest, developers should strive to have as large a clinical trial as possible and include a control arm; in situations where this is less feasible, objective outcome metrics should be used that, ideally, align with available historical control data.

Market access: The conversation on appropriate market access coverage in rare diseases is still evolving. However, developers should be prepared to demonstrate how performance on clinical trial end points translates to clinically meaningful outcomes and, ultimately, utility to patients (i.e., QALYs). Key sticking points include the onset and durability of treatment benefits in cost-effectiveness analyses. As we've seen for Luxturna, the intuitive appeal of a potential one-time cure must be backed by clinical data supporting long-lasting efficacy — otherwise, pricing and reimbursement may suffer.

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