PRECISION ADVANCE the cell & gene therapy collective™

The Price is Right: Cell and Gene Therapy Approvals and Market Access in 2023

cell&gene day 2023

The Price is Right: Cell and Gene Therapy Approvals and Market Access in 2023

Pricing strategies, evidence generation, and value demonstration to payors all significantly impact market access and commercial success for cell and gene therapies. In the clinical development of a cell or gene therapy, early health economic evidence development and market access planning is important when demonstrating value to payers and health technology appraisal (HTA) organizations. In a dynamic regulatory and market access landscape, balancing the requirements of regulators and the expectations of payors can be challenging since there is no one-size-fits all approach.

To explore this and other cell and gene therapy sector priorities, Precision ADVANCE, the Center for Breakthrough Medicines, and the Alliance for Regenerative Medicine co-sponsored the second annual Cell & Gene Day, hosted by Endpoints News, on May 11, 2023. Throughout this event, over 25 successful innovators from across the advanced therapy sector shared fresh ideas and insights on overcoming critical challenges in bringing life-saving therapies to patients in need.

This white paper is based on a discussion moderated by **Phil Cyr**, Senior Vice President of Precision Value & Health, and the following panelists:*

Christopher Kurtz, MD, Chief Medical Officer, Kate Therapeutics
Kate Therapeutics is focused on adeno-associated virus (AAV)-based gene therapies for treating genetically defined muscle disease. Given the off-target effects and high doses often associated with AAV-based gene therapies, the company is developing capsid and cargo technologies for tissue-specific delivery.

Francesca Cook, Vice President, Pricing and Market Access, REGENXBIO
REGENXBIO is a gene therapy company that has developed a NAV® Technology Platform comprised of over 100 novel AAV vectors. Currently, the company has products in pivotal trials for Hunter syndrome and age-related macular degeneration and in Phase 1/2 trials for Hurler syndrome and Duchenne muscular dystrophy (DMD).

Oswald Bentinck, Vice President, Global Head of Value & Access, Rocket Pharmaceuticals
Rocket Pharmaceuticals received Regenerative Medicine Advanced Therapy (RMAT) designation in February 2023 for its AAV-based gene therapy for Danon disease, a rare genetic disorder characterized by cardiomyopathy, making it the first cardiac gene therapy to receive this designation.

Francis Pang, Senior Vice President, Global Market Access and International Geographic Expansion, Orchard Therapeutics
Orchard Therapeutics is focused on treatments for neurodegenerative diseases using their ex vivo autologous gene therapy platform. In 2020, the company gained approval for a gene therapy product for metachromatic leukodystrophy, a rare and life-threatening neurogenerative disease. Currently, the company is developing other neurodegenerative disease assets and seeking to harness their technology for more prevalent diseases such as Crohn's disease and frontotemporal dementia.

Determining value and price for cell and gene therapies

Companies often spend significant time trying to figure out how to best evaluate their drug from the standpoint of value. Cyr set the stage for a dynamic discussion by asking the panelists how they decide which factors need to be considered in determining optimal reimbursement, price, and approach to the market, health technology assessment (HTA) assessors, and payors. When valuing a product, it is essential to look at the current landscape and ask:

- What is the current unmet need?
- How does the product address that need?
- What is the product's value and benefit above and beyond what is currently available?

For gene therapies, the potential for one-time, durable therapy could truly be transformative for patients. However, Cook emphasized that affordability is a challenge, so it is also important to examine cost-effectiveness and budget impact for payors, as well as coverage and reimbursement trends globally.

It is worth noting that there are differences between what is required for market entry in different parts of the world. In the US, companies can enter the market upon regulatory approval, beginning the process of pricing the product and demonstrating its value. Whereas in the EU, HTA assessors have, in some cases, requested data on added or incremental benefit following regulatory approval and prior to market entry.

For successful market access, it is critical to consider all the factors above, ensuring that product value is demonstrated through clinical trial data and real world evidence. It is also important to capture the patient experience through patient-reported outcomes and to consider caregiver burden. Developing a holistic perspective on the different aspects necessary to support overall value will give sponsors insight into what pricing could look like and what reimbursement will be needed to achieve commercial success.

Bentinck explained that timing is also a factor when defining pricing. Early on in product development, pricing estimates may be based on analogues as outcomes data is not yet available and it is not yet clear which patient population is most likely to gain benefit. As data accumulate, it becomes possible to start building models to get a better for what a value-based price would look like.

The existence of a comparator may also facilitate a cost offset argument. For example, onasemnogene abeparvovec (Zolgensma) was launched at a price of $2.1 million, making it a very high-cost one-time therapy. Still, a cost offset argument could be made since the 10-year cost of nusinersen (Spinraza), another disease-modifying treatment for spinal muscular atrophy, is approximately two times more in the US.

WHILE THE COST OFFSET ARGUMENT IS COMPELLING, MOST gene therapies LACK A CLEAR COMPARATOR

1. Lakdawalla DN, Phelps CE. Health Technology Assessment With Diminishing Returns to Health: The Generalized Risk-Adjusted Cost-Effectiveness (GRACE) Approach. Value Health. 2021;24(2):244-249.

While the cost offset argument is compelling, most gene therapies lack a clear comparator. Payer research and health economic modeling can help in determining a cost-effective price at the inflection point of the various cost effectiveness thresholds in different countries. Pang pointed out that, in recent years, there has been increased interest in the value flower, which highlights elements such as equity or the value of hope that may be overlooked or underappreciated in conventional drug value assessments (see Figure 1), and the Generalized Risk-Adjusted Cost-Effectiveness (GRACE) framework, which suggests that optimal cost-effectiveness thresholds should be proportional to disease severity.[1]

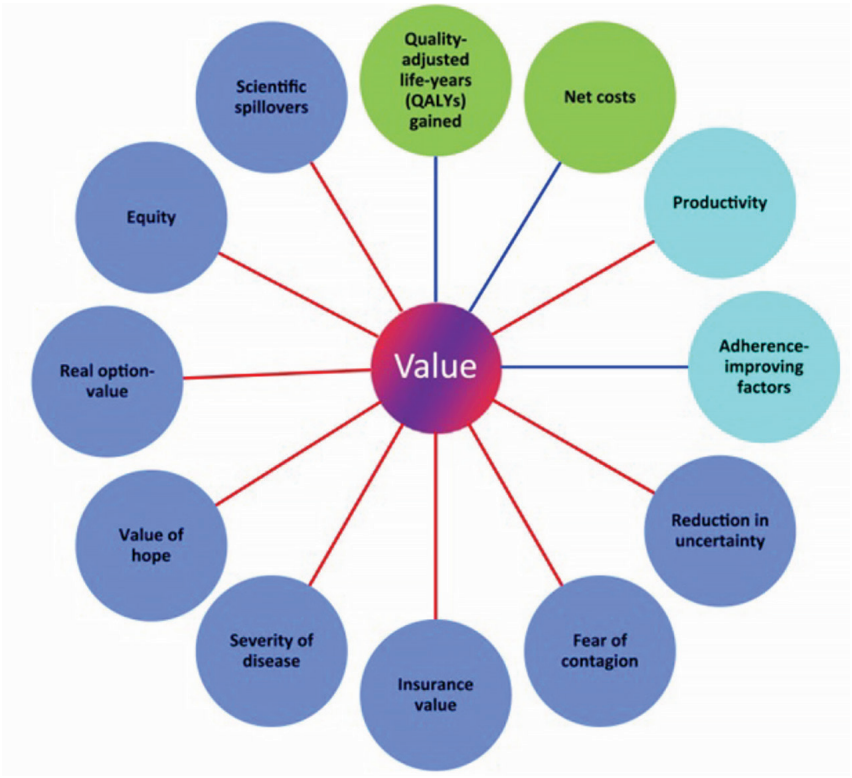

Figure 1. Elements of the value flower[2]

Generating evidence for regulators and payors

Thinking about access throughout the clinical development continuum can help sponsors generate the evidence necessary to support not only regulatory submissions, but also successful commercialization and reimbursement. It is important to define upfront the geographies in which studies may be conducted to ensure that clinical trial design meets muster in all regions. Dr. Kurtz commented that, in programs where a single study forms all of the evidentiary basis from first in human through registration, it may be necessary to incorporate endpoints for payor reimbursement planning that may not be the central endpoints for registration. These additional endpoints have operational implications on patient and site burden.

2. Lakdawalla DN, et al. Defining Elements of Value in Health Care—A Health Economics Approach: An ISPOR Special Task Force Report [3]. Value Health. 2018;21(2):131-139.

Given that gene and cell therapies may require long-term follow up, Cook shared a strategy of using healthcare resource utilization as an endpoint to support the value proposition of durability. In addition, a study by the National Institute for Clinical Evidence found that cell and gene therapies and rare disease products were associated with high quality-adjusted life years (QALYs), which can serve as a measure of treatment benefit.

If data useful for reimbursement has not been collected during clinical trials, Pang suggested that sponsors can look at aspects of the value chain that can be executed in the time available before regulatory approval and reimbursement, such as health economic modeling, claims data analysis, caregiver surveys, utility generation, and structured literature reviews.

As cell and gene therapy developers turn their attention to more chronic and more prevalent diseases, evidence generation may be even more complex. Dr. Kurtz pointed out that "for very prevalent indications, the evidentiary bar is going to be higher" and it is also going to be a challenge to manufacture enough drug to run trials, much less support commercialization and access. Advanced therapies targeted at more common diseases will also have more comparators, and single-arm studies may no longer be sufficient. For more prevalent diseases where there are already approved therapies, evidence generation needs to focus on identifying an unmet need, bringing in real world data to support that need, and demonstrating how a one-time durable therapy addresses that need. Demonstrating durability may also be an effective approach to differentiating from existing chronic therapies and supporting the overall value proposition for cell and gene therapies.

Applying innovative reimbursement models

Cyr then turned the conversation to innovative reimbursement models. As a group, the panelists agreed that there is a general willingness and openness among payers to alternative payment schemes for advanced therapies, especially if outcomes are observable in routine clinical practice. In terms of adjudication, there are two primary pay-for-performance frameworks: payment by results and payment at results.

There are significant differences between how reimbursement models are applied in the US and in the EU. In the EU, there are single payers who typically project five years or less into the future but now need to account for potential lifetime benefit. Certain EU countries, such as Germany, may require manufacturers to apply for add-on payments to cover cell and gene therapies.

In the US, there are not only a multitude of payors, but also commercial patients who move from one insurer to another, making it challenging to follow patients over the long term to see whether outcomes are being met. Other issues in the US include the Medicaid best price policy, which may limit value- or outcomes-based models, and diagnosis-related group (DRG) reimbursement or bundled payment implications for therapies that require inpatient administration.

Bentinck shared his experience with the launch of Zolgensma, where there was a lot of early engagement with payors on the feasibility of splitting payments over time or making annuity payments and what outcomes to track. Unlike many other gene therapies, which look at surrogate endpoints, Zolgensma is tied to clear milestones—the ability to roll over, sit, stand, and walk—that can be tracked in the real world. Still, Bentinck stated that EU payers often said, "Well, this is too complicated. Just give us a discount." Nevertheless, several split or annuity payment schemes were

implemented in the EU. In the US, due to patient mobility between insurance plans, reimbursement models tended to look only at survival and the need for permanent invasive ventilation since these outcomes were easiest to track within the healthcare system.

Understanding unique access considerations for cell and gene therapies

Launching a cell or gene therapy is very different from launching a conventional medicine. With a conventional medicine launch, especially in the EU, the goal is typically to secure reimbursement in as many countries as possible within 12-18 months.

Launching

A CELL OR GENE THERAPY IS VERY DIFFERENT FROM LAUNCHING A CONVENTIONAL MEDICINE

"I think you have to be more thoughtful…when it comes to cell and gene therapy," said Pang. With cell and gene therapies, there are usually a limited number of treatment centers in key countries that are capable of—or qualified to—administer the product. Thus, reimbursement applications would be submitted only in those countries and cross-border healthcare would need to be considered for patients who live elsewhere. In the EU, there is a cross-border directive that can be harnessed for patients from countries outside of those with treatment centers. Similarly, in the US, access to cross-state care is possible with Medicaid, as long as the treatment center is credentialed with the Medicaid program in which the patient lives.

Early access programs also differ between advanced therapies and conventional medicines. For conventional medicines—especially for chronic, prevalent conditions—it may be possible to offer the product free at the outset and then to commercialize it after securing reimbursement. With one-time gene therapies, Bentinck explained that early access reduces the pool of eligible patients that can be commercialized later. This represents a significant challenge to offering no-cost early access. A few countries, such as France, have rules in place for paid early access.

The future of market access for cell and gene therapies

Cyr concluded the discussion by asking the panelists what they are excited about or what they hope to see in the future with cell and gene therapies. Their responses ranged from a desire to see increased acceptance of uncertainty at registration or increased flexibility by payers in looking beyond the current budget cycle to cautious optimism about the imminent development of sustainable financing solutions that will increase access.

**The views and opinions expressed in the context of this discussion are those of the panelists and do not necessarily reflect those of the official policy or position of their respective companies.*

PRECISION
ADVANCE the cell & gene therapy collective™

PRECISION for medicine | PROJECT FARMA | PRECISION value & health

ADVANCE, a collection of interconnected services and complementary teams, uniquely focuses on the complexities of clinical, regulatory, manufacturing, and commercial needs to successfully bring cell or gene therapies to market.

Connect with one of our experts. Contact us at **precisionadvance@precisionmedicinegrp.com**.
To learn more about Precision ADVANCE, visit **precisionmedicinegrp.com/advance**.

2 Bethesda Metro Center
Suite 850
Bethesda, MD 20814

Rev. 01