Innovation: Shortening the Path to Commercialization in Advanced Therapies

PRECISION ADVANCE the cell & gene therapy collective™

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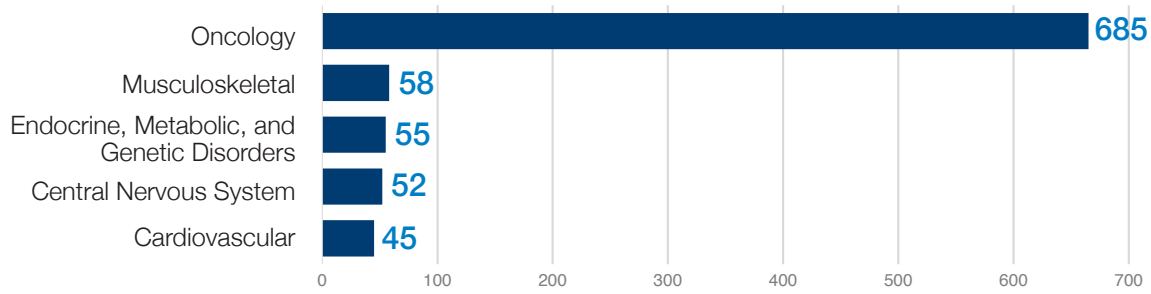
Shortening the Path to Commercialization in Advanced Therapies

More than 1,000 regenerative medicines and advanced therapies are in clinical trials worldwide, according to the Alliance for Regenerative Medicine. Such robust research activity reflects the exponential growth of the pharmaceutical industry's drug development pipeline, which includes numerous emerging gene and cell therapies. Bringing such advanced products to market requires a comprehensive and integrated approach.

Earlier this year, Precision ADVANCE, the cell & gene therapy collective™, hosted "Innovation: Shortening the Path to Commercialization in Advanced Therapies," an expert panel discussion moderated by Clare Sarvary Fourrier, Senior Vice President of Operational Strategy at Precision for Medicine. Precision ADVANCE is a suite of interconnected services and complementary teams focused on the complexities of gene therapies and the resources needed to bring these advanced therapeutics to market.

Figure 1: **Top 5 Advanced Therapy Clinical Trials Currently Underway Worldwide**



Source: Alliance for Regenerative Medicine. 2020: Growth & Resilience in Regenerative Medicine Annual Report. https://alliancerm.org/sector-report/2020-annual-report.

Asking the Right Questions

Successful commercialization begins and ends with asking the right questions. "There are no silver bullets, [and] I don't think there's any established best practices," noted Parag Meswani, Chief Commercial Officer at Sio Gene Therapies, who previously led the US commercialization and launch of Luxturna® (voretigene neparvovec-rzyl) while at Spark Therapeutics. He said any company that seeks to reduce the complexity of commercialization needs to ask some fundamental questions, starting with why: "Why should a physician prescribe you gene therapy? Why should a patient take that gene therapy? Why should a payer pay for that therapy?" Such basic questions "are even more critical when you're talking about a potential one-time delivery of a therapeutic."

Fortunately, the industry now has clearer regulatory guidance for developing and commercializing cell and gene therapies. "It's here, it's tangible, and it gives us something to grab onto, and something to strive for," Meswani said. This new framework helps innovators evaluate chemistry, manufacturing, and controls (CMC), study design and endpoint selection, regulatory perspective, and what is meaningful to a patient which allows the industry to factor in "what matters" to answer the "why" question across all stakeholders.

"Companies launching cell and gene therapies should view the overall supply value chain as a critical strategic concern that should be considered before the commencement of clinical trials," Meswani observed. That, he suggested, is the time to conduct a detailed analysis of the end-to-end delivery of gene therapy at commercial scale, and to assess a company's knowledge of the patient journey.

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—Parag Meswani,
Chief Commercial Officer,
Sio Gene Therapies

Leveraging Technological Advances

Anshul Mangal, President of Project Farma and Precision ADVANCE, cited the emergence of single-use, disposable technologies as vital to improving the speed and productivity of advanced therapy manufacturing while also lowering production costs, energy use, water consumption, and—critically—the risk of cross-contamination. He also noted that improvements in infrastructure technologies enable more flexible manufacturing, allowing companies to "scale better and faster" and reduce time to market. Shifting from dedicated facilities to more multimodal facilities "will allow greater flexibility, scalability, and operational efficiency and speed to market," he commented.

Scaling Up to Meet Demand

There can be no successful commercialization without product availability. The successful transition of cell and gene therapies from the clinic to the marketplace largely depends on the scale-up of manufacturing to generate and satisfy global demand. "For a clinical trial, we often need only a few batches to meet demand," noted Dave Lennon, President of Novartis Gene Therapies. "But when we move into the manufacturing scale, we're thinking about global reach, we're thinking about continuous production and continuous supply of product, and we're thinking about changes we're going to make to the process for these advanced therapies."

Scale-up is particularly important for allogeneic cell therapies, which rely on healthy donors. "You have to scale-up the process to really deliver on the promises of allogeneic, which are easy access, low cost of goods, and better control, because you can really control the starting material in a way that is not possible with autologous cell therapy," explained Pascal Touchon, President and CEO of Atara Bio. Although scale-up of this magnitude can be challenging, it is achievable.

Keeping Patients Engaged

On the road to commercialization, the intricacies of cell and gene therapy development and delivery require trial sponsors to be creative when engaging with clinical sites and in laying the groundwork for an overall positive patient experience.

“A wholesale understanding of the patient population and their individual, physical, and emotional journey through diagnosis and treatment is essential across the different stages of drug development,” noted Meswani, who stressed the importance of including “the patient voice” in early discussions of trial design, treatment considerations, outcomes selection, burden of illness, and patient support. In the pre-treatment stage, active engagement with patients and caregivers can inform communications with the patient community and physicians. Post-treatment, deep and continuous patient insight can help shape the sustained follow-up that regulators and payers will require for monitoring long-term outcomes.

“The regulatory role doesn’t end once a product is on the market,” Meswani reminded the panel, citing the need for continued safety monitoring, active and passive surveillance, and review required for phase 4 studies. “If advanced therapies fulfill their promise to meaningfully modulate or even eradicate disease, the patients who are feeling better may prefer to disengage from the fact that they’ve even had a condition. And so how do you maintain that connectivity and keep them as active members of a gene therapy or a disease community and capture that critical long-term data?”

The solutions, Meswani said, “need to be frictionless and innovative in the way they’re deployed to maintain patient engagement and access to data and to the connectivity of that data to longer-term outcomes.” Monitoring solutions must therefore place the patient mindset at the center, as patients must be able to understand the expectations around monitoring. With such safeguards in place, companies can “enable the right tools of communications to capture that data over the longer term.”

Real-World Evidence

Maintaining patient engagement and capturing study data are core to demonstrating value. Open-label study data can sometimes be sufficient to secure regulatory approval for a cell therapy, provided the data demonstrate a very high level and duration of response in an area of unmet medical need. However, as Touchon observed, payers may “see with different eyes, and they say, ‘Okay, but this is relatively short term; you don’t have a comparator. Is this really something that cannot be achieved with something else?’”

That is where real-world evidence comes in. “In oncology, for example, you may not have any product approved, [but] there is still a standard of care because physicians are trying the most they can to solve the issues with their patients and save their lives,” Touchon commented. Robust data on such patients can enable a comparison of “the patients they’re treating in the real world with a patient you have in your study. That’s where you can convince the payers that you’re bringing really significant benefit on top of what’s existing today.”

“But that relies on the quality of your real-world evidence,” continued Touchon. “And then, of course, you have to follow [with] the real-world evidence of your product.” He cited long-term data from a

Kymriah® (tisagenlecleucel) study in which patients who responded 1 or 3 months post-therapy were still responding 5 years later. Such long-term evidence may spark discussions with payers over "which assumption you should make about the long term, when you don't have long-term data," he said. "You need to have real-world data progressively demonstrating that the initial assumptions about the 5 or 10 year benefit are real."

"Real-world evidence and health economic models can be important for informing the sorts of parameters in the evidence thresholds that you need to hit, not just with the clinical trials, but also informing any gaps in your evidence," commented Alex Grosvenor, Senior Vice President of PRECISIONadvisors, Precision Value & Health. "It's multifaceted, especially when we're talking about rare diseases [that] are often not very well understood, not very well characterized. From the payer perspective, a lot of this information-gathering and analysis is essential for all of the downstream development and commercialization, especially when it comes to health technology assessments (HTAs) and submissions."

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Meswani remarked upon the need for "broad-stroke" companies to continue to identify innovative mechanisms to quantify and demonstrate the long-term value of gene therapy. "I think there's a different burden of proof that's emerging between rare disease gene therapies and therapies that are being developed for more prevalent conditions. We're still kind of learning as we go."

Developers of therapies for rare and more prevalent conditions share "a deep appreciation of the burden, prevalence, and impact of the disease on patient communities," Meswani continued. "That is best understood through understanding the lens of the patient." Although it is critical to quantify the socioeconomic impact of rare disease, "the actual cost of managing a disease and being able to quantify that is probably more easily done on the prevalent condition side, depending on medication." Addressing these considerations "will build a narrative that will inform physician and payer understanding and can ultimately be incorporated into HTA submissions and economic models that support the value dossier."

Finally, when demonstrating value, it is important to understand the payer mix. "The US has a very clear delineation of payer mix, and that informs how you think about strategy on the market access side," Meswani noted. "In Europe, it's probably a more regional or locally driven process. Again, that's probably consistent for rare and prevalent indications."

Pricing and Market Access

Cell and gene therapies are very different from conventional chronic treatments, a fact that makes some of the industry's current models for value assessment, pricing, and reimbursement of advanced therapies "not quite fit for purpose," according to Grosvenor. Although some pricing and reimbursement authorities around the world have adapted to accommodate these new treatments, "that is an ongoing evolution," he said. "One thing that's important to think about is just why or how gene therapies are different."

When cell and gene therapies are given as “one-and-done” treatments, “that cost is in the upfront administration of the treatment, unlike chronic therapies where the cost is spread over the course of the treatment duration,” Grosvenor stated. He added that these innovative treatments require highly specialized administration in specialty centers, potentially leading to funding and local access issues.

Nevertheless, Grosvenor expressed optimism about recent progress in this area. “We’re still in the early days, of course, but we’re seeing that the HTA bodies, for example, in Europe are recognizing the value of these treatments. Where there is a very high unmet need, they are seeing through the limitations of the clinical evidence, relying on very strong efficacy signals, and translating and recognizing the value that these treatments bring. So far we’ve seen lots of positive decisions. And I think where we’re going will be interesting, because we’re going to be expanding into more common diseases where some of the affordability, budget impact, and evidence requirements may differ. So it’s very much a case of ‘watch this space.’”

To help developers bring about the next transformation in advanced therapy, the interdisciplinary teams at Precision Medicine Group—including Precision for Medicine, Project Farma, and Precision Value & Health—deliver a comprehensive, integrated approach to driving clinical, manufacturing, and commercial success.

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Precision 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.**
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