The promise of gene therapy and considerations for dosing strategies

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As gene therapy companies continue to make tremendous strides in developing breakthrough treatments, with landmark approvals for conditions such as hemophilia, these highly innovative therapies are laying the groundwork for further development. As sponsors press on with R&D and preparations for regulatory submissions, questions are surfacing about dosing profile and strategy in manufacturing, pricing, market access, and competitive positioning. One key challenge revolves around decision-making for "one-and-done" (O&D) versus redosing therapies.

By "one and done," we refer to a gene therapy expected to require a single administration for lifetime efficacy. We'll use "redose" to refer to a gene therapy with efficacy that is long-lasting but expected to require subsequent doses during the patient's lifetime. Let's take a look at some of the issues involved.

Which model is better for manufacturers to pursue?

Ultimately, the science and clinical data dictate what dosing frequency is most appropriate, rather than any commercial considerations. What do the models tell you about the durability of the effect? What does durability look like in clinical trials? However, more and more sponsors will face commercial decisions about gene therapies in development before true durability can be known. If early signals are unclear, it might be advisable to commit to a redosing approach early on, as there are some underappreciated commercial benefits. Ultimately, however, relative value comes down to market- and product-specific considerations.

If durability looks promising during clinical trials, what are the main benefits of an O&D approach?

One of the primary advantages of this approach is the convenience for the patient, who is freed from chronic treatments. It is also a distinct competitive advantage to position the therapy as a durable solution.

Are there examples of a successful O&D treatment in the marketplace, and if so, how have manufacturers managed issues related to pricing and market access?

There are examples of single-dose therapies that have showed strong and lasting benefit in clinical studies, as well as therapies that have proven steady-state improvement at two years. However, as with any new product, the cost is high, and long-term efficacy is unproven. Without a longer-term picture, there remains a possibility that the effects could wane over time, meaning payers face substantial financial risk in the traditional buy-and-bill model. Thus, sponsors have devised new paradigms for pricing to ensure access.

These include, for example:

- Outcome-based contracts and rebates, where the sponsor shares risk if outcomes fail to meet a specific threshold, relieving the payer of responsibility for payment or offering a rebate.
- Payer-provided administration, where the payer, rather than the treatment center, purchases and administers the treatment, with the sponsor assuming costs and risks involved in shipping and storage.
- Installment payments over time rather than a single up-front cost – although this model is quite challenging in the U.S., given how the healthcare system works and the Medicare best-price rules.

What are some of the implications for manufacturing?

Whether the O&D or redosing approach is indicated, one of the most critical decisions for a gene therapy company relates to building out the infrastructure required for full-scale manufacturing versus engaging with a contract development and manufacturing organization (CDMO). Understanding the likely dosing profile can help inform the volume unit requirements and corresponding manufacturing requirements. Well-documented processes and analytical methods become very important in determining the right course of action.

The expected dosing profile and resulting manufacturing capacity requirements represent one of many factors to consider when deciding to manufacture in-house versus outsource. And while engaging a CDMO might appear to be the fastest and perhaps least risky solution, the timelines required for contract negotiations and slot reservations represent a significant factor.

Please note, for O&D therapies, there will likely be a need to scale capacity up quickly to treat the prevalent population and then down dramatically to serve the incident population. To mitigate this challenge, the manufacturer can feasibly convert bioreactors and other manufacturing components to other products.

Why are sponsors exploring technologies enabling redosing?

Answering this question returns us to the issue of durability and proving long-term efficacy. Some of the most promising therapies intended for a single dose have demonstrated uneven expression and declines at each update. The lack of a clear plateau has hampered enthusiasm and raised concerns from a regulatory standpoint.

What are the pros and cons of the redosing approach?

While there are no redose gene therapies currently on the market to help us with definitive insight, we can make a few assumptions about this model. With the right strategy and plan, there are potential advantages over the O&D approach, beginning with pricing. With a lower list price and additional payment due at the point of subsequent dosing, and hence lower upfront cost, there is less risk for payers. Redosing can make low-incidence orphan disease markets more sustainable. And an early commitment to a redosing model could simplify some aspects of pricing and market access.

Further, redose therapy can tout optionality for future treatment decisions, which can have strong appeal to physicians. While not as convenient as O&D, redosing is more flexible, and the uncertainty about durability is addressed from the outset.

That said, the redosing profile and proportion of patients eligible for redosing can dramatically impact the year-over-year manufacturing capacity required. Many open questions remain, beginning with determining the redosing technology best suited for a given therapy, the proportion of patients eligible for redosing, and the timing for subsequent doses. Regulatory submissions demonstrating redosing feasibility and justifying the redosing timeline will present a challenge, along with the clinical trial design.

What about competitive considerations?

For redose therapies, if there is already an O&D product on the market, the addressable market will be smaller. For O&D products, on the other hand, redose therapies can undercut on price. In any case, competitive threats exist for both dosing profiles, particularly for later entrants to orphan indications.

Ultimately, decisions will depend on indication, competitive dynamic and manufacturing capacity. At Parexel and Health Advances we can help companies overcome roadblocks and navigate this complex landscape, wito deliver these promising therapies faster to the patients who need them.

To learn more, download our Cell & Gene Therapy eBook or connect with one of our experts today.

Meet our experts

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Vivek leads Health Advances' Gene Therapy Practice and has experience with all aspects of gene therapy, including manufacturing, clinical trial design and commercial strategy. His expertise includes portfolio planning and new opportunity identification across therapeutic areas, with a specific interest in ophthalmology, orphan/genetic disease, and oncology.

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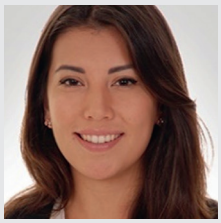

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