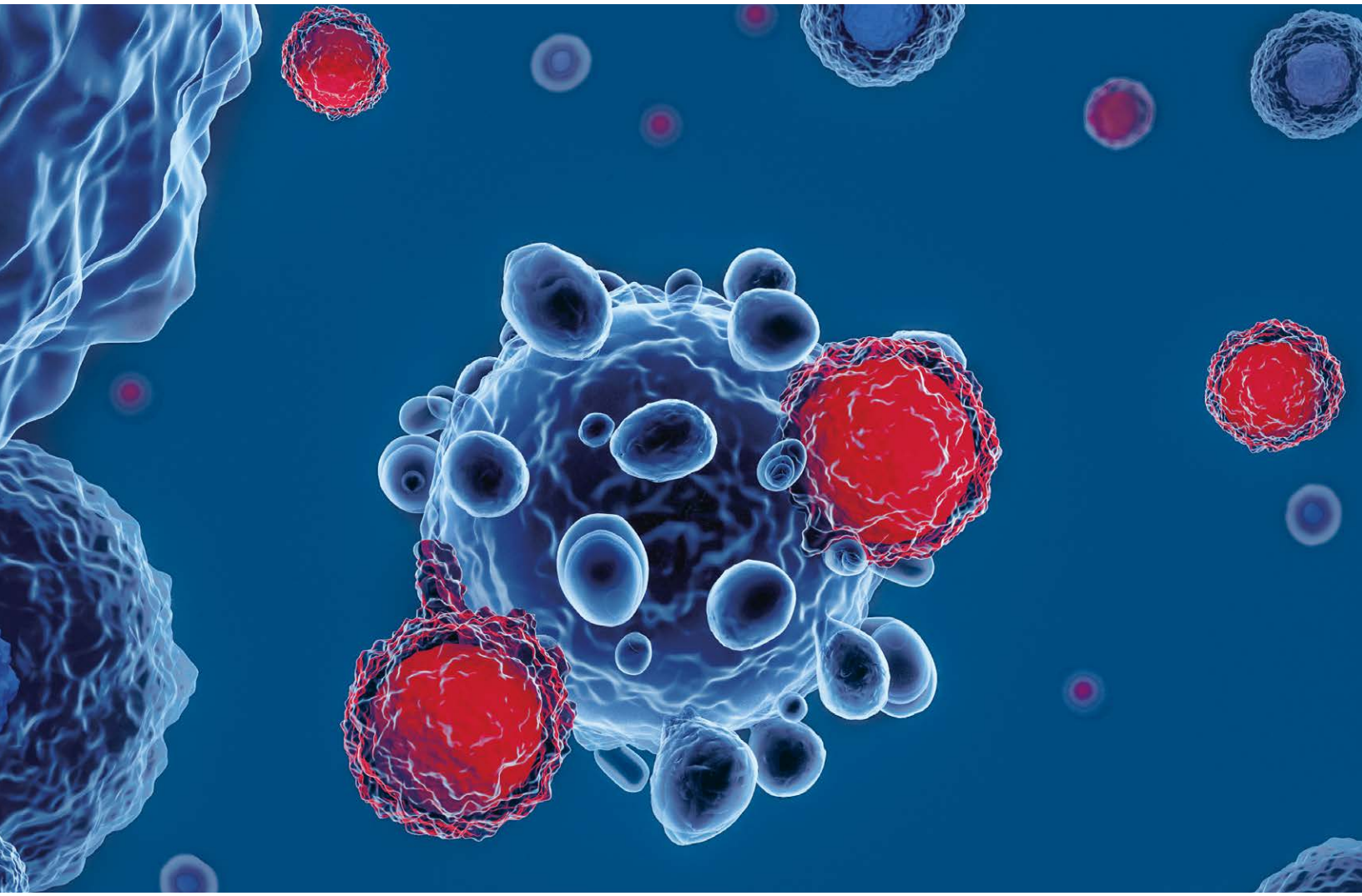
avantor™

Advancing gene therapy by solving challenges in scale-up & manufacturing



As the biopharmaceutical industry sharpens its focus on gene therapy, opportunities for advancements and challenges in manufacturing processes still remain. While the industry has made progress to effectively treat and control diseases based on regulatory approvals for novel therapies, the industry needs to continue to find efficiencies and optimize manufacturing processes in order to deploy gene therapies economically and at scale.

Dr. Ger Brophy, executive vice president of biopharma production at Avantor, offers insights on how the biopharma industry can evolve its processes through lessons learned from manufacturing monoclonal antibodies (mAbs) or vaccines, improving supplier collaboration, and other factors.

We've heard a lot over the past year about cell and gene therapy–two of the most exciting medical innovations with the potential to cure some pediatric cancers and other life-threatening or previously incurable diseases. What successes did the industry see over the past year, and what challenges are still ahead?

Genuine progress is being made in the long-standing battle to effectively treat and control disease, as evident with some of the first regulatory approvals for new therapies of their kind and the M&A activity within the pharmaceutical industry we witnessed in 2019.

For gene therapies, specifically, we've seen that approvals so far have been for rare diseases with relatively small patient groups:

- In Europe, Bluebird's treatment for Beta thalassemia, a form of anemia, was approved by the European Commission (EC) for use with patients 12 years of age and older. [1]
- In the United States, treatments for Biallelic RPE65 mutation-associated retinal dystrophy, a form of blindness [2], and spinal muscular atrophy (SMA), a disease that affects around 25,000 children and adults in the United States [3], were both approved by the FDA. These treatments were developed by Spark and AveXis, respectively, two companies that were subsequently acquired by much larger players: Spark by Roche and AveXis by Novartis.
- Kite, acquired by Gilead, has seen positive results as it seeks to extend its Yescarta® label, a treatment for certain types of non-Hodgkin lymphoma, into relapsed or refractory indolent (slow growing) non-Hodgkin lymphoma.
- And the licensing agreement that came at the end of 2019 between Roche and Sarepta to launch and commercialize a gene therapy addressing Duchenne muscular dystrophy (DMD) [4] only solidifies big pharma's interest in this growing space. This will bring the sophistication of label and geographic expansion strategies to bear on these therapies in 2020 and beyond.

Focus will also turn to reimbursement: If reimbursement does not continue to support such expensive treatments widely, it could limit investment in the space. In the United States, so far it appears promising that commercial insurers and Medicaid support reimbursement, although patients still face challenges in receiving approval for treatment. The discussion about reimbursement is ongoing in Europe.

However, 2020 will prove to be challenging: the COVID-19 pandemic has temporarily disrupted the pace of research and approvals of new gene therapies related to cancer and other conditions. We're seeing delays to clinical trials across the board; not only for gene therapies but all molecules, and from small to large biotech firms. 1,273 trials and counting were reported as on hold as of the end of May, impacting well over 200,000 people and 573 companies. However, we are currently setting a new, historic pace at which new therapies are being taken from research to full-scale manufacturing. This may set a precedent for the future to help with fast-tracking cell and gene therapies, as well.

What are the most promising targets within gene therapy, and what are some of the challenges in commercializing them?

While the approvals for treatments for rare diseases are certainly early wins, the impact of gene therapies will significantly expand as approved treatments are administered to larger patient groups and studies expand to address diseases that are broader reaching—for example, with treatments for multiple myeloma, leukemia and other forms of cancer.

At the Alliance for Regenerative Medicine (ARM) Cell and Gene Therapy "Meeting on the Mesa" event last fall, the significant response and survival rates from patients with Diffuse Large B-Cell Lymphoma, Acute Lymphoblastic Leukemia, Non-Hodgkin's Lymphoma and Spinal Muscular Atrophy were noted and discussed. Treatments for these diseases involve at least two different approaches: ex vivo and in vivo.

CAR-T cell therapies are essentially ex vivo gene therapies in their mode of action. The patient's own T-cells are modified with a viral vector and re-administered to the patient. This mode of action underpins treatments like Kymriah®, a treatment from Novartis for treating acute lymphoblastic leukemia, as well as Yescarta® from Kite.

In vivo gene therapies, by contrast, take an engineered molecule and administer it directly to the patient in either a systematic or targeted way. Zolgensma®, developed by AveXis (a subsidiary of Novartis) for the treatment of SMA, involves an infusion of an engineered virus which spreads to the entire patient's body. Luxterna®, developed by Spark (a subsidiary of Roche) for the treatment of Biallelic RPE65 mutation-associated retinal dystrophy, is also administered directly to the patient but is targeted to the patient's individual eye.

Regardless of the method, scalability and manufacturability are the two closely related challenges the industry faces, especially if gene therapies are to fulfill their clinical potential. At first, the questions to be answered appear quite challenging. For example, can we manufacture cell and gene therapies at scale? If we can, then can we do so safely and at a reasonable cost so patients may access the treatments?

It's a very different challenge when compared to manufacturing a monoclonal antibody, as an example. There is no inventory of the product; the patient is waiting for the treatment as it is being customized for them. This makes the risk/reward balance very different, and it requires companies to think about drug products in a different way.

There are many process challenges associated with manufacturing gene therapies. What are your views as far as three of the most significant ones to resolve that would bring about the greatest benefits to moving the industry forward?

Across the board, we need to implement improvements in raw material inputs and innovations in manufacturing technology in order to deploy gene therapies economically and at scale.

First, the numbers in production don't add up. Adherent and packaging systems are inefficient. If you look at the gene therapy viral vector levels, the magnitude of the therapy being delivered to the patient, in increments from E6-E16, shows that the industry simply does not have the ability to produce enough to satisfy growing demand.

Either something has to change with the process itself, or massive manufacturing capacity will need to continue be built to sustain current production methods. For example, in Astellas's recent acquisition of Audentes, analyst comments indicated that in addition to the clinical assets Audentes brought, their fully integrated AAV manufacturing capacity was driving a lot of the value. [5] In the meantime, there will be significant reliance on contract manufacturing organizations (CMOs) for capacity: we've seen this recently with a partnership announced by Ultragenyx Pharmaceutical Inc. and Daiichi Sankyo Company, Limited, for example. [6]

The second challenge that comes to mind is process standardization. Variables and failure modes must be taken out of the process—this is where innovations in process technology can make a real difference.

Production systems can be standardized and closed so they're less exposed to failure modes. Processes can be miniaturized to drive cost efficiencies and, perhaps, better clinical outcomes. We can employ better workflow technologies, such as single-use sterile fluid transfer. It is also probable that fill/finish requirements will be different for cell and viral products, so improved excipient technologies will play a large part in better patient experience and response.

Different analytical standards will also apply, particularly in relation to adventitious agents during cell expansion.

What are some of the major gene therapy production components that impact optimization potential?

There are two major routes: First, we have to anticipate innovation and optimization coming through from advances in academia. Second, we expect step changes in process improvements from contract development and manufacturing organizations (CDMOs) and other producers. This can be done with closely monitoring, and where relevant even partnering with, these organizations early on, as well as through involvement in consortiums and professional organizations like Rx360 or DCAT.

In raw materials, specifically, we are seeing more requests for cGMP grades of materials which have never needed to be made at scale or to cGMP specifications before. Even if these are available at the correct analytical grade, there is considerable raw material expense associated with components such as plasmid DNA.

The requirement for biological activity to be retained limits the use of harsh purification methods and adds a special sensitivity that potentially harmful or adventitious agents cannot be introduced through the raw material supply chain. This is an area that greatly benefits from close partnership between manufacturers and their raw material suppliers, to better understand the requirements for cGMP materials

"Across the board, we need to implement improvements in raw material inputs and innovations in manufacturing technology in order to deploy gene therapies economically and at scale."

and use them early on in the therapy development and manufacturing process.

Producing the viral vectors used to deliver the therapeutic treatments is a complex process with multiple points of potential failure. What do manufacturing companies need to consider to make the process more efficient?

Efficacy goes hand in hand with safety. Efficacy of the treatment at a dose which does not trigger the cytokine storm of CRS, or only at a level of CRS which can be managed with steroid or other anti-inflammatory drugs, is a major challenge.

One area where efforts are being made to improve efficacy is through so-called tissue targeting, which works to improve how much of the therapeutic payload reaches the diseased cells.

In theory, viral vectors offer an attractive solution to tissue targeting through the selection of serotypes. However, some of the serotypes with the highest targeting efficiency may be harder to produce at high titers.

What are the key differences – and similarities that can be leveraged – from manufacturing mAbs versus gene therapies?

Despite the compelling clinical results from autologous CAR-T treatments, the distributed nature of the process and ongoing issues with cell expansion steps have raised concerns about the scalability of these treatments. For gene therapy, the nature of drug substance is more similar to what we're used to seeing in traditional biologic drugs, like monoclonal antibodies, vaccines and recombinant proteins.

Some tools for creating both cell and gene therapies are similar, including single-use bioreactors and fermentation media and supplements. But even here, there are differences. One example is the impeller set up needed to optimize production from suspension cell lines.

We are also seeing increased customer sensitivity to fermentation components such as fetal bovine serum and its country of origin. Given the nature of the downstream process and the requirement to preserve biological activity, there is a growing desire to minimize the potential introduction of adventitious agents through raw materials in upstream processes. And there are manufacturing methods and components that have not previously been used in regulated processes, such as cesium chloride density gradient centrifugation, new forms of size exclusion and affinity chromatography.

Industry regulations are still in development as we know, and we are seeing some regulatory bodies fast-tracking approvals in special circumstances. What should biopharma manufacturers do to ensure a smoother process as a treatment progresses from early to commercial stages? How can suppliers help their customers better navigate approvals?

I think there is real opportunity for producers in working earlier with raw material suppliers, especially in navigating the specific level of cGMP needed for raw materials and single-use landscapes.

As both a materials and single-use manufacturer, Avantor is uniquely positioned to help customers determine where to adopt technical, quality and regulatory best practices from manufacturing established therapies, like monoclonal

antibodies or vaccines. Whether it's characterizing raw materials to see how trace metals can impact downstream processing, reducing risk through the use of aseptic single-use technology for sampling, or evaluating and implementing cGMP materials early on to help expedite scale-up—there are certainly lessons to be learned.

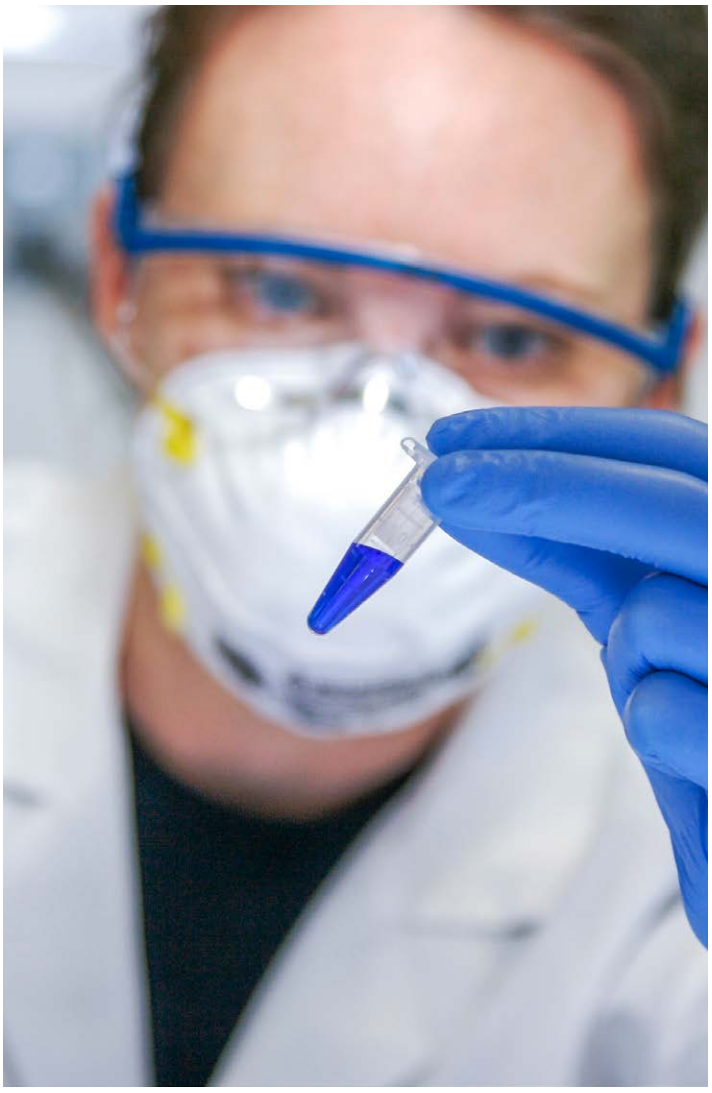
Developing partnerships with providers as soon as possible should increase process efficiency and minimize later missteps, even on joint approaches to regulators. Additionally, it helps for tracking and measuring a raw material supplier's quality system to ensure consistency over time. Breakdowns in QMS can be catastrophic, so the importance of collaborations and quality agreements with raw materials suppliers cannot be understated.

Finally, what are your visions in terms of next-generation technologies and/or process developments?

Gene therapy manufacturers and the suppliers that support them need to develop stronger partnerships. In areas such as cell culture components, production chemicals, single-use technologies, sterile fluid transfer, excipients and the technology surrounding those process components, there is value to trying new solutions to address improving the manufacturability of these therapies.

Even at the early stages of trials, we can better understand the variability that comes from research data, and use it to correlate with clinical and process outcomes. Taking out manual steps as early as possible is important, as well as creating closed systems using sterile fluid transfer technologies to eliminate process risk.

Overall, it's an exciting time. We can anticipate expanded programs in basic research in order to develop, understand and



"As both a materials and single-use manufacturer, Avantor is uniquely positioned to help customers determine where to adopt best practices from manufacturing established therapies, like mAbs."

characterize new drug targets. This should drive an innovative program of clinical development married to improvements in process technologies. Both of these will ensure this will be a constantly evolving landscape, and we need to be ready to address the challenges ahead.

ABOUT THE AUTHOR

Dr. Ger Brophy,
Executive Vice President, Biopharma Production, Avantor
Manager, New Product Development

Dr. Ger Brophy is Executive Vice President, Biopharma Production. In his current role, Dr. Brophy is responsible for developing and implementing Avantor's Biopharma Production offering to support the current and future needs of our customers. Prior to joining Avantor, Dr. Brophy held a variety of research and development, strategy, advanced systems, and business development positions with GE Healthcare Life Sciences, GE Healthcare Medical Diagnostics and Amersham for nearly 30 years. Dr. Brophy earned a Bachelor of Science in biotechnology, as well as a doctorate in molecular biology from Dublin City University in Ireland.

43939-AB-JS

ZPROAVTR43939-EN