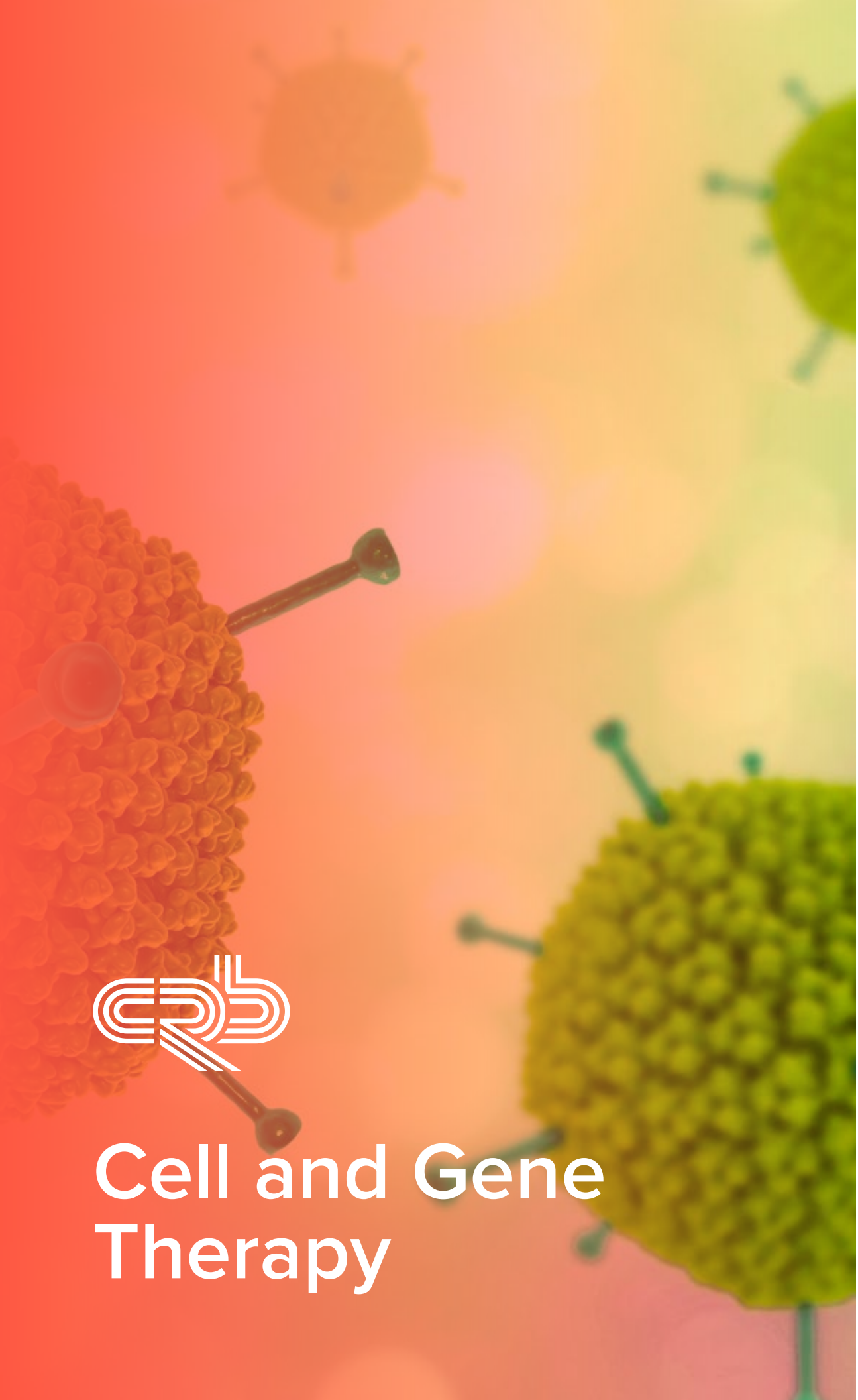

Cell and Gene Therapy

HORIZONS

AUTHORS

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About this Report

Our world has entered a new decade filled simultaneously with uncertainty and opportunity. The COVID-19 pandemic has changed our lives in so many ways, from how we work and learn to how we socialize and relate to each other. And for those whose professional lives are spent toiling against both today's health threats and those to come, the virus has magnified the challenges — and possibilities — faced by our world's vaccine and medicinal therapy infrastructure.

Anchored by the insights gained through a survey of nearly 150 industry leaders, our inaugural *CRB Horizons: Cell and Gene Therapy* report finds the biopharma space at an important inflection point. An industry laser-focused on rapid growth and speeding lifesaving therapies to patients is too often weighed down by outdated processes and age-old concerns of budget and resources. A special challenge, our report finds, lies in how manufacturers can pivot nimbly as competition, shifting market demands and emerging diseases require multiple product pipelines and the ability to move seamlessly between them.

We went a step further by asking our group of subject matter experts — some of the most respected in the space — to listen to those industry responses and think prescriptively about where the market is headed. They analyze the processes, manufacturing efficiencies and solutions that will govern how critical therapies reach patients. The resulting vision is of an industry future-proofed by new, agile and cost-effective manufacturing processes, and thus better prepared to meet our world's varied and unforeseen health threats head on.

We welcome your feedback through our contact page at crbgroup.com, and we wish you a happy and safe 2021 and beyond.

Ryan Schroeder
President, CRB

Emerging ATMP Trends:

Defense Against Disease Requires New Nimbleness

By: Noel Maestre and Peter Walters

A peculiar thing happened along the journey of cell and gene therapy: For an industry accustomed to packing years of change inside a single financial quarter, tomorrow's critical therapies — aimed at thwarting a host of emerging health threats, including a global coronavirus pandemic — remain curiously reliant on the equipment and manufacturing processes of years gone by.

The biotech boom of the 1970s and 1980s gave us many of the open, manual and antiquated processes that we too often find in many of today's advanced therapy medicinal products (ATMP) research and development labs as well as regulated manufacturing environments supporting good manufacturing practices (GMP) late-phase clinical products — processes that rely heavily on human operators. Although these processes are used in cutting-edge investigations, they're based on outdated and unscalable methods (scale-out vs. scale-up) that are increasingly under heavy regulatory scrutiny. We often consider the hypothetical scenario of a cleanroom operator sitting at her biosafety cabinet — fine for clinical research, but incredibly risky at commercial scale.

Yet, this inaugural CRB Horizons: Cell and Gene Therapy report — built on the survey responses of nearly 150 ATMP industry leaders — finds an alarming dependence on the sort of primitive technology and manual applications that, in their day, made sense for an industry looking to grow quickly and leanly. But as we head into 2021, the combination of open processes with a high potential for human error, antiquated technologies, and research-facing technology ill-suited for commercially facing applications creates business risk at a time when market demand for the

rapid delivery of patient therapies is rising. It's also a time when the COVID-19 pandemic has raised provocative questions about the ability of vaccine and therapy infrastructure to meet the challenge.

Operating space design and layout considerations are vital to the evolution of cell and gene therapy, and responses across our survey reveal gaps in that growth. For instance, while nearly three-quarters of respondents indicate automation is impacting operations, nearly one-third report using Grade A biosafety cabinets (BSC) in a Grade B cleanroom — a clear sign of the need to embrace innovation.

Across this report, CRB dives deep into an array of important issues confronting the ATMP space, finding an industry brimming with optimism for the future but uncertainty about the path ahead. The pain points of resource and risk are ever-present.

More than half of our survey respondents say they expect to adopt a multimodal solution within the next two years, with flexibility, scalability, operational efficiency and speed to market as the top drivers.

Our team of CRB subject matter experts explore a number of topics, including:

MULTIPLE MODALITIES

Manufacturers and contract manufacturing organizations (CMOs) face the same stark reality: Flexibility is required to nimbly address shifting needs in the marketplace. CMOs must respond to ever-evolving client needs and manufacturers who are bringing their ATMP production activities in-house, have complex product pipelines, and need the flexibility to develop different modalities in parallel. More than half of our survey respondents say they expect to adopt a multimodal solution within the next two years, with flexibility, scalability, operational efficiency and speed to market as the top drivers.

65%

of respondents say they're developing (or intend to develop) stable producer lines because of lower material costs and more scalable processes.

GENE THERAPY MANUFACTURING

Propelled by favorable regulatory winds and high demand for novel and in-demand cell and gene therapies, viral vector manufacturing is poised for a significant jump, with some estimates predicting up to 20% year-over-year growth through 2025. More than 80% of our respondents say they rely on transient transfection to manufacture viral vectors from packaging cells, but a new host cell line — stable producer lines — is gaining momentum, with 65% of respondents saying they're

developing (or intend to develop) this type of vector host cell because of lower material costs and more scalable processes.

FACILITY OPTIMIZATION

Nearly 80% of survey respondents ranked process development and optimization among their top three commercial manufacturing challenges across both cell and gene therapy platforms. A majority of survey respondents also cited variability/uncertainty in their process among primary operations concerns, with regulatory considerations close behind. More than a third said they're concerned or anxious about their facility's achievable throughput.

PROJECT DELIVERY

Two-thirds of respondents would consider a turnkey, or end-to-end, approach to project delivery that moves them from design to operation. But when asked about their barriers to adopting a turnkey approach to project delivery, nearly a third cited a lack of organizational awareness of end-to-end offerings in the marketplace. Other inhibitors include constrained procurement processes and belief among some that single-source solutions create excessive risk.

REGULATORY

The key to navigating cell and gene therapy's often complex regulatory environment is understanding ATMP regulations, embracing closed bioprocessing and communicating with regulatory agencies and industry peers. Respondents said they comply with the most important regulatory guidance documents in Europe and the U.S. In Europe, 27% comply with Part 4 of Eudralex, a summary document that is considered the best current guidance document on the production of ATMPs.

GENETICALLY-MODIFIED CELL THERAPY

A majority of respondents are uncertain whether they will switch to a gene-modifying technology in the near future. Overall, 15% of respondents are anticipating a technology switch within the next three years. Respondents are significantly more likely to rank process development and optimization above other factors as top challenges in progressing toward commercial manufacturing. Notable is the vast majority of respondents who say they're pursuing CMOs or contract development and manufacturing organizations (CDMOs), with more than half indicating limited existing manufacturing capacity as the top driver for outsourcing production.

The drive for optimization

A key theme recurs across our survey: Manufacturers need to design and construct flexible facilities that can accommodate both automated processes and production's evolutionary changes to help them produce a range of cell and gene therapies. But respondents indicate they need help in meeting the challenge; only a few

facilities have been built and less than one-quarter said they were looking at in-house commercial production. More than three-quarters of respondents said they were planning to partner with CMOs/CDMOs, but even those organizations lack the necessary manufacturing capacity.

There is a clear need for support in the design, planning, delivery and optimization of flexible facilities. The industry was very much in a research and development phase when genetically-modified cell therapies were first tested to see if they would work in people. When they did, organizations moved forward with lab-based platforms because, prior to that, no commercial market existed to require scalability or development of dedicated GMP-compliant ATMP processing technologies.

The need for manufacturers to design and construct flexible facilities that can accommodate both automated processes and production evolutionary changes to help them produce a range of cell and gene therapies.

Fast forward to now, when a necessary truth governs the marketplace: Our industry requires more advanced equipment technology that closes and automates manufacturing processes as much as possible. In turn, this creates another uncomfortable reality: The more humans are removed from the process, the faster products can move through pipelines, while lowering risk and manufacturing costs.

But it's not that easy. The required technology is novel enough that much of it hasn't yet been proven outside of the process development lab, and few organizations have been eager to volunteer to test the efficiency. A solution is the emergence of a process technology specialist who can assess good manufacturing practices for new equipment platforms.

These design and engineering specialists focus on ATMP facility design, with a mix of stochastic and deterministic simulations and process closure and automation technology. They join with manufacturers and operating companies to understand the risks and opportunities of new and emerging technology, such as a facility's expected throughput and the needs or limitations of its operators.

Moving toward such partnerships will result in future facilities that can pivot quickly in a global health environment that puts a high premium on flexibility and efficient technology. The COVID-19 pandemic has exposed a troubling lack of preparedness to shift quickly from clinical vaccine trials to large-scale production. The flexible spaces envisioned by a multimodal manufacturing approach, however, would provide those crucial benefits for a world constantly on the defense against disease.

The Challenges of Manufacturing Cell and Gene Therapies at Scale

By: Allan Bream and Brita Salzmann

Biopharmaceutical manufacturing has undergone a revolution in the past decade, progressing from blockbuster, one-size-fits-all drugs to the manufacture of biotherapeutics that treat small groups of patients or, in some cases, one patient at a time. Chief among these are ATMPs, research-intensive medicines of which more than 1,000 potential therapies are progressing through clinical trials toward commercial manufacturing.

1,000

potential therapies are progressing through clinical trials toward commercial manufacturing

Cell therapy involves either taking cells from a patient, genetically modifying those cells, and returning them to the same patient (autologous) or using gene-modified cells from an unrelated donor to treat multiple patients (allogeneic). These novel therapies offer potential treatments to what have been incurable conditions, including autoimmune disorders and cancers.

Despite the excitement about these treatments, there are significant challenges that face this nascent sector, as identified by the survey data:

- Lack of commercial GMP manufacturing capacity to meet current and future demand
- A need to automate and optimize processes
- Open and manual operations are difficult to scale, driving the need for closed, automated processing at the commercial scale
- A transition from adherent cell culture to suspension cell culture to maximize scalability
- Lack of skilled and available expertise to manage and operate new process equipment

The survey data reflects the need for manufacturers to design and construct flexible facilities that can adapt to future process improvement and technologies that continue to change every two to five years. It is this evolving optimization that will allow manufacturers to prepare for the need to scale up or scale out to GMP commercial manufacturing to meet future demand.

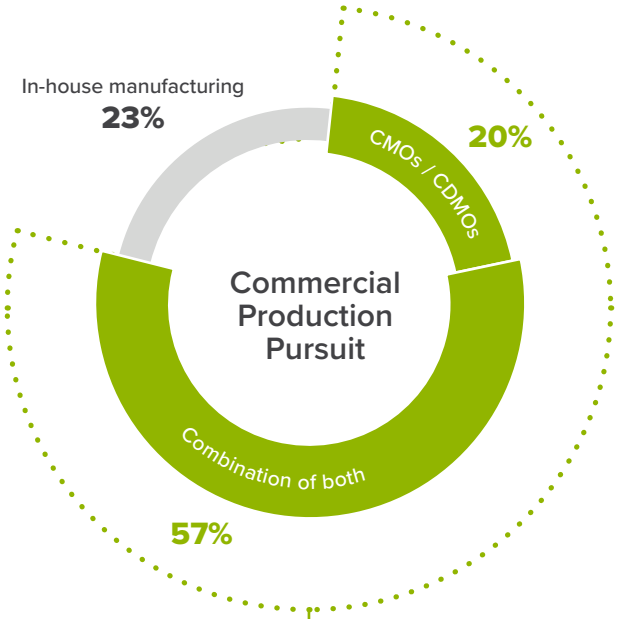
GREATER COMMERCIAL GMP MANUFACTURING CAPACITY IS NEEDED

Unsurprisingly, nearly three-quarters of respondents are partnering with CMOs/CDMOs to meet these challenges, with many pointing to a lack of CGMP manufacturing capacity as their main reason to outsource (see Figure 1). This isn't necessarily a cut-and-dry solution, however. CMOs are experiencing the same capacity crunch that's affecting the rest of the industry, resulting in wait times that can stretch a year or more. To meet growing demand, CMOs/CDMOs also need to consider flexibility as they invest in new facilities.

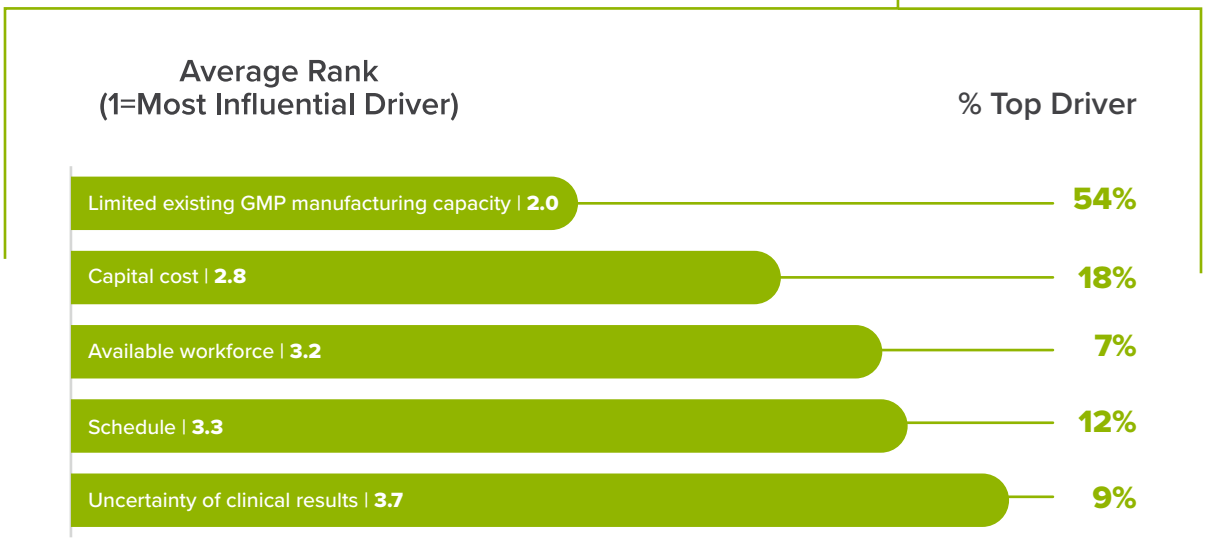
Lack of a skilled and available workforce was another significant consideration, which is understandable given the highly technical developments in this sector in the past decade. We've seen this phenomenon repeat during the birth of every high-tech industry over the past 60 years, including recombinant DNA technology in the 1970s and 1980s. The early entrants skew towards PhD-level staff, which is also occurring with ATMPs as companies try to translate benchtop techniques to a robust commercial environment. This takes highly skilled, highly trained people to get products off the lab bench and into the cleanroom. CDMOs can provide this expertise, but they will also be faced with the challenge to source a skilled workforce.

FIGURE 1

Q1: In your progression toward commercial production, are you planning on pursuing: [Single Select]



Q2: You indicated that you are planning on pursuing a CMO or CDMO as part of the manufacturing process. What are the drivers for that decision? [Rank Order: 1=Most influential driver—5=Least influential driver]



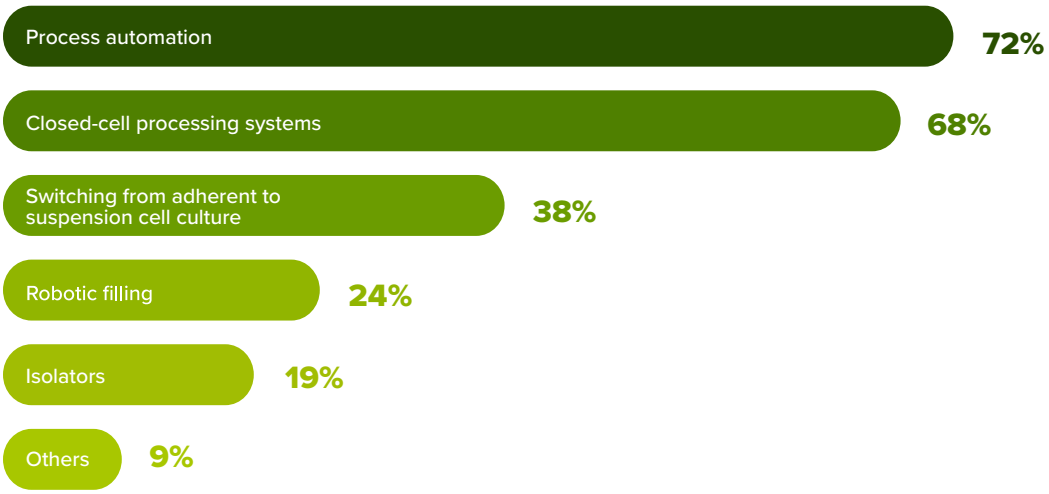
Source: CRB

PROCESS AUTOMATION AND CLOSED PROCESSING SYSTEMS ARE ANTICIPATED TO BE THE MOST IMPACTFUL TECH ADVANCEMENTS

The need for aseptic manufacturing is what drives the most impactful tech advancements, according to survey respondents. A majority of respondents listed process automation (72%) and closed-cell processing systems (68%) as the most significant technological advancements that will affect their decisions about the manufacturing process (Figure 2).

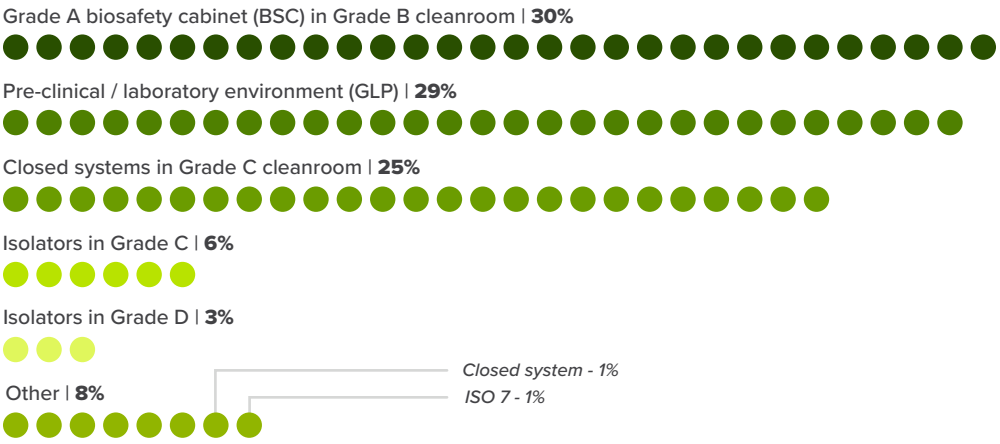
FIGURE 2:

Q1: Which near-term technology advancements do you foresee most impacting your manufacturing process? [Select all that apply]



Source: CRB

Q2: What type of cleanroom environment are you using to produce your therapies?



Source: CRB

Process automation is a key consideration for respondents because whole-cell processing and purification are technique-sensitive processes with a high potential for failure. Because cell therapies are introduced intravenously and can't be terminally sterilized, the whole-cell processing that is required during manufacturing must be done under aseptic conditions to reduce the risk of contamination from the manufacturing environment, raw materials or other critical factors. Any slight alteration in a process or human error can jeopardize an entire batch destined for a waiting patient.

Equally important to respondents was the adoption of closed-cell processing systems, which offer numerous advantages to get novel therapeutics to patients safely and effectively. Reducing touchpoints in the process can minimize or eliminate the risk of contamination. It also leads to a potential reduction in cleanroom requirements: While closed systems in Grade C cleanrooms now account for 25% of cleanroom environments, we anticipate that number to increase to close to 75% within a few years. Closing and automating processes improves speed, quality control, design flexibility and the path to regulatory approval.

Designing flexible ATMP facilities comes with unique challenges that depend on the type of therapy that is being made. For example, autologous facilities must be designed with chain of custody top of mind since they are vein-to-vein treatments for a single patient. In this case, quality control labs occupy more floor space as each batch, while small, must be tested. And, when increasing the production of autologous cell therapies, the process must be scaled out, not up, to add more throughput capacity. Batches of allogeneic treatments, on the other hand, require less quality testing space and can be scaled up volume-wise as they contain many doses to treat many patients. Flexible designs will account for challenges unique to the type of therapy, including future automation and technology advancements so manufacturers can avoid a costly retrofit or expanding the facility footprint.

Grade C cleanrooms now account for

25%

of cleanroom environments; we anticipate that number to increase to close to

75%

Switching from adherent to suspension culture, whenever possible, is also expected to impact the manufacturing process (38%) (Figure 3). This is an important consideration given the limited production scale and manual manipulations of the anchorage-dependent cell cultures. Suspension cultures allow more automation early in the process and can surpass adherent culture volume limitations, which is desirable for allogeneic cell therapies, thus increasing production.

In contrast to the current use of manual filling techniques, respondents anticipate adopting robotic filling (24%) will facilitate scale-up and adding isolators (19%)

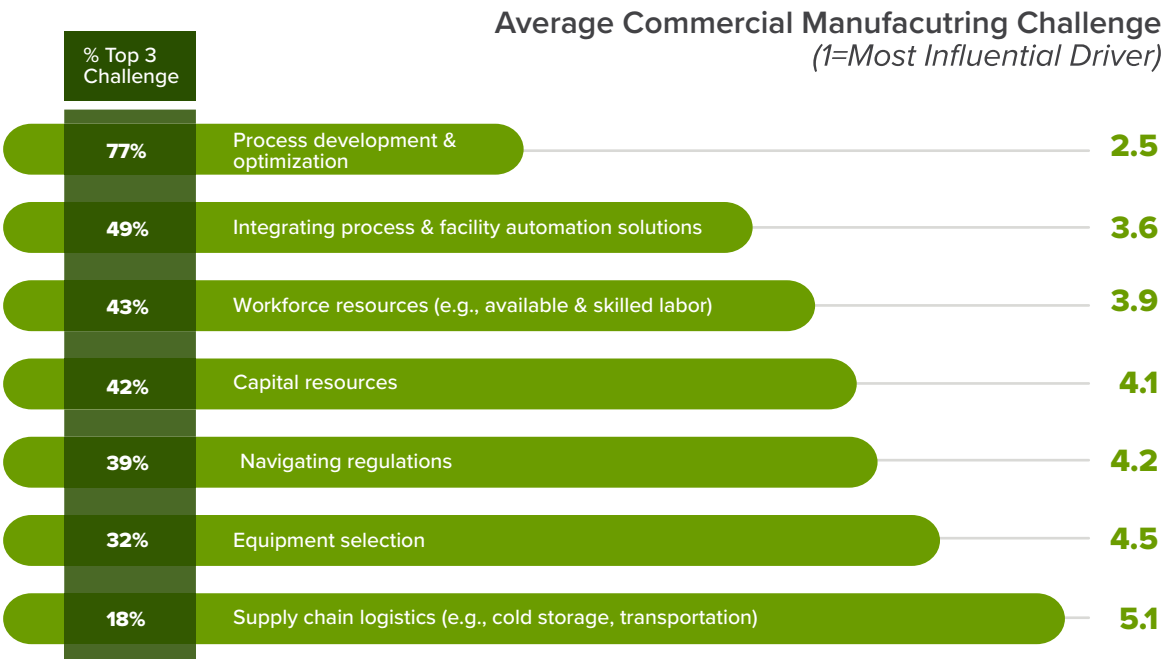
will reduce the square footage of highly classified spaces to a box within a room. Isolators, which provide an aseptic environment as an alternative to a closed system, can eliminate the use of Grade A BSCs (30%), decreasing operational costs when accommodated by lower room classification. ATMP isolators have a different look and feel than the isolators traditionally used in large-scale filling operations. These more compact, tailored versions fit the ultimate objective to design a closed process. However, these isolators are a heavy capital investment and can become costly when considering custom designs.

PROCESS DEVELOPMENT AND OPTIMIZATION RANKS AS THE BIGGEST CHALLENGE TO COMMERCIAL MANUFACTURING

So much technology in the journey from clinical to commercial manufacturing is new — within the last 10 years — that it's easy to understand why process development and optimization was the biggest concern among respondents (Figure 3).

FIGURE 3

Q1: What do you consider to be your biggest challenges in progressing toward commercial manufacturing? [Rank Order: 1=Most critical challenge—7=Least critical challenge]



Source: CRB

The cell processing equipment used for small-scale production for research and clinical trials is likely to have open connections requiring a Grade A environment with Grade B background HVAC classification for protection. This approach does not lend itself to supplying thousands of patients per year, stressing the importance of a transition to closed processing systems that can operate in a Grade C or lesser environment. The speed of change in this sector means companies have only had a couple of years to learn and exploit all this innovation. To scale up or scale out from the open, manual processes that are used during clinical production to commercial manufacturing would require a substantial increase in headcount and floor space, at a cost that would be prohibitive.

15%

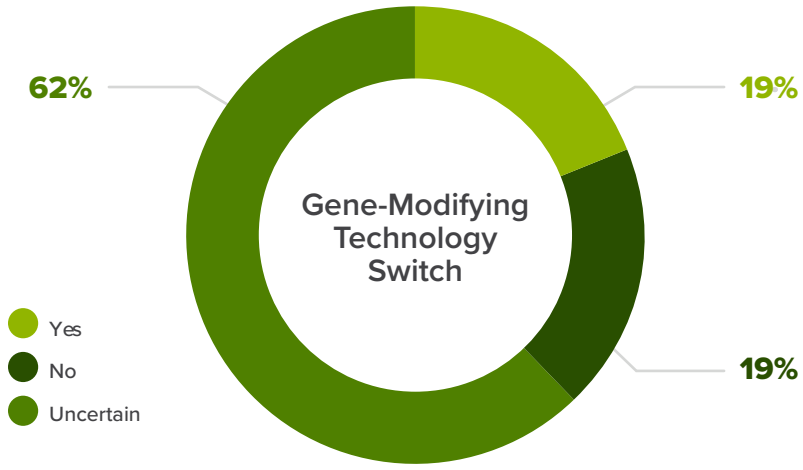
of surveyors anticipate they will switch to another ATMP in the next three years

As mentioned previously, attracting skilled and available labor was also noted as a significant challenge for the shift to commercial manufacturing. The adoption of new techniques requires an influx of expertise and equipment that manufacturers are still trying to understand and perfect. Take the gene-modifying platforms that are used. Manufacturers of both autologous and allogeneic genetically-modified cell therapies primarily rely on viral vectors (79% and 74%, respectively). These first-generation vehicles that deliver altered genetic material to cells are more popular than more recent developments, including mRNA (35%) and gene-editing (CRISPR or TALEN) technologies (28%). While there is a high level of uncertainty about whether they will switch to another ATMP platform, 19% anticipated switching and 15% said this will happen within the next three years (Figure 4). There will always be a place for experience with viral vectors, but these more recent platforms require employees with different skills. These platforms also use different processes that take time to develop and apply rigorously and faithfully so they provide consistent results.

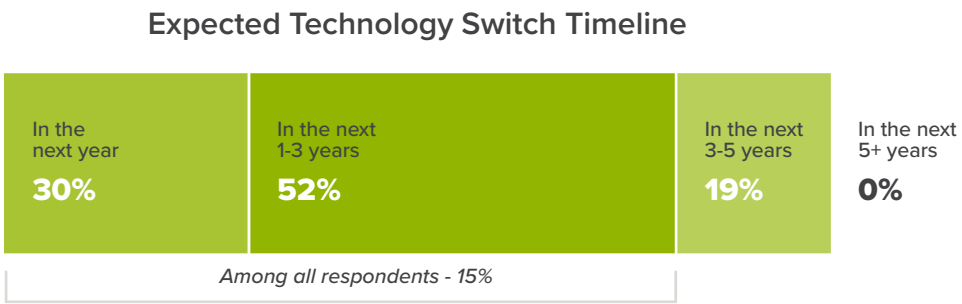
It is imperative when considering the design and function of a commercial-scale ATMP plant, to focus on closed, automated, commercial-scale technology and design.

FIGURE 4

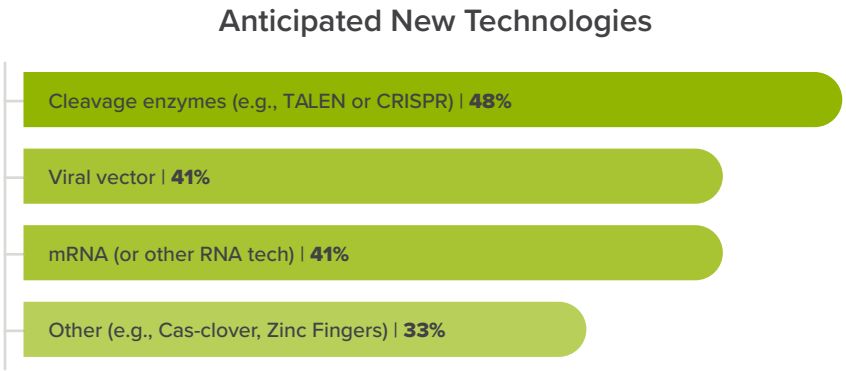
Q1: Do you anticipate switching to another gene-modifying technology in the near future? [Single Select]



Q2: How soon do you anticipate switching to another technology? [Single Select]



Q3: What technologies do you anticipate switching to? [Select all that apply]



Source: CRB

Planning for flexibility in process and facility design

Given the challenges with commercial-scale manufacturing that survey respondents identified, it is imperative when considering the design and function of an ATMP facility, to focus on closed, automated, and scalable technology. Flexibility in site and facility design is essential to account for emerging equipment innovations and to make room for tomorrow's therapies.

Ideally, this forward-thinking approach will allow manufacturers to strategically adopt breakthrough technologies and new automation solutions, giving them both the control and the adaptability they need to shape the future of cell and gene therapy.

You Say You Want a Revolution:
The Promise of Multimodal Manufacturing

By: Noel Maestre and Peter Walters

In 1965, the editors of *Electronics* magazine asked for contributions to a series called “The Experts Look at the Future.” One of those experts, Intel’s Gordon Moore, submitted a gutsy article that claimed computing power would double every two years. “I find the opportunity to predict the future in this area irresistible,” he told his editors.

Fifty-five years later, the phone in your pocket testifies to the accuracy of what we now know as Moore’s Law, and the report you’re reading shows that some of us still can’t resist the chance to forecast what’s ahead. Like Moore, we see exponential growth on the near horizon, only in our case, it’s not computer power that’s surging — it’s the power of a new approach to cell and gene therapy manufacturing. And it’s about to change everything.

*We see exponential growth on the near horizon, only in our case it’s not computer power that’s surging — it’s the power of a new approach to cell and gene therapy manufacturing. **And it’s about to change everything**.*

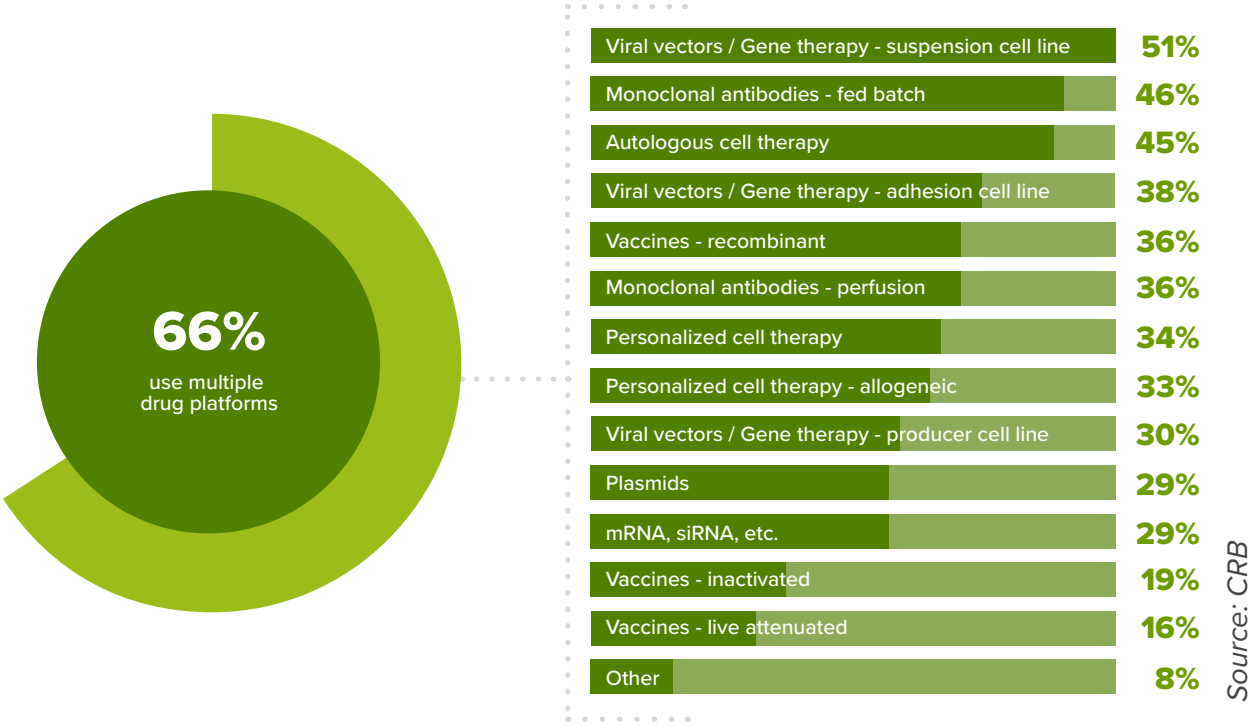
THE COMPLEXITY OF ATMP PIPELINES

Unsure of which modalities will move successfully through clinical testing, today's ATMP manufacturers are playing a numbers game by investing in diverse and complex product portfolios. Our survey respondents reflect this trend; two-thirds are developing more than one drug platform, with viral vectors and monoclonal antibodies (mAbs) dominating (Figure 5).

FIGURE 5

Q1: Is your company's product pipeline comprised of multiple drug platforms (i.e. modalities and/or variances)? [Single Select]

Q2: What platforms and/or modalities are being considered? [Select all that apply]



Source: CRB

A complex product portfolio is manageable during early development, but how will these manufacturers navigate advanced clinical testing and, eventually, commercial production? The dedicated facilities that are common today aren't well suited for this challenge; they were designed to solve a different kind of problem, giving companies the means to manufacture a single type of product predictably and efficiently. Pivoting to another product is a lengthy and expensive enterprise, requiring major facility modifications and a complex tech transfer.

Today's ATMP companies are struggling to adapt this legacy model to suit a market that expects more personalized and diverse therapies. Some are building and expanding single-purpose facilities, hoping that their calculated risk will pay off; others are turning to CMOs for extra manufacturing capacity, where they're stymied by lead times of 16 months or more.

This can't go on. To realize the full potential of this phase shift in manufacturing, we need more than incremental adaptations and stopgap solutions. We need a seismic change in the way we design, program and operate our manufacturing facilities.

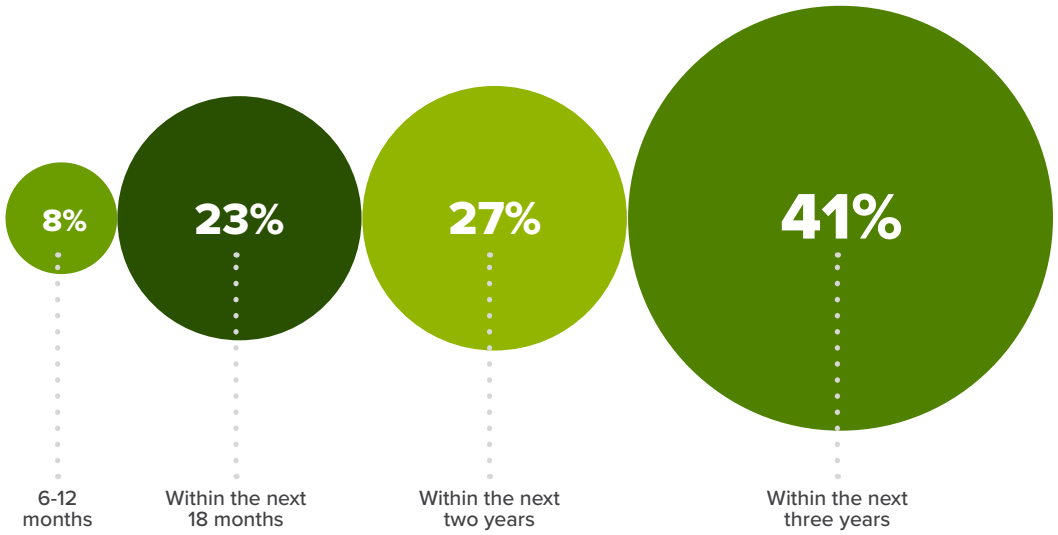
THE MULTIMODAL REVOLUTION

Like most revolutions, this one will arrive gradually and then all at once. The "gradual" chapter has been underway for some time, with ATMP platforms evolving from nascency to full acceptance in the mainstream clinical environment. This has prompted a recent explosion of mergers, expansions and new enterprises, which brings us to a flashpoint in the history of pharmaceutical development: multimodal biotech and ATMP manufacturing, a fringe concept only a few years ago, is about to take over.

Nearly 60% of our survey respondents plan to adopt a multimodal solution within two years (Figure 6). We predict that this number will come close to 100% in less than a decade. It won't be easy; shifting from a dedicated facility to a facility in which multiple modalities are developed in segregated, side-by-side production suites

FIGURE 6

Q1: What is your projected timeline for the adoption of a multimodal solution (either multimodal flexible suite or dedicated suites)?

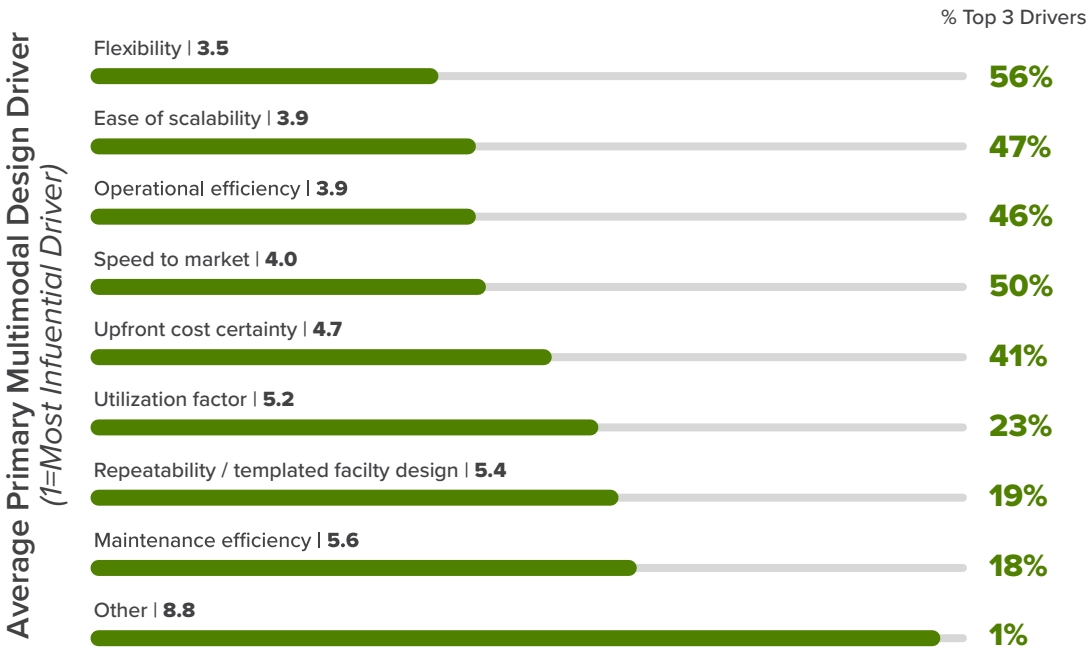


Source: CRB

will challenge how owners, quality departments, regulators, facility designers, and people from all corners of the industry perceive cell and gene therapy manufacturing. But with this challenge comes the lasting rewards of improved flexibility, ease of scalability and better cost control (Figure 7).

FIGURE 7

Q1: What would be your organization's primary drivers for adopting multimodal design solutions? [Rank Order: 1=Most influential driver—9=Least influential driver]



Source: CRB

A QUICKSTART GUIDE TO MULTIMODAL

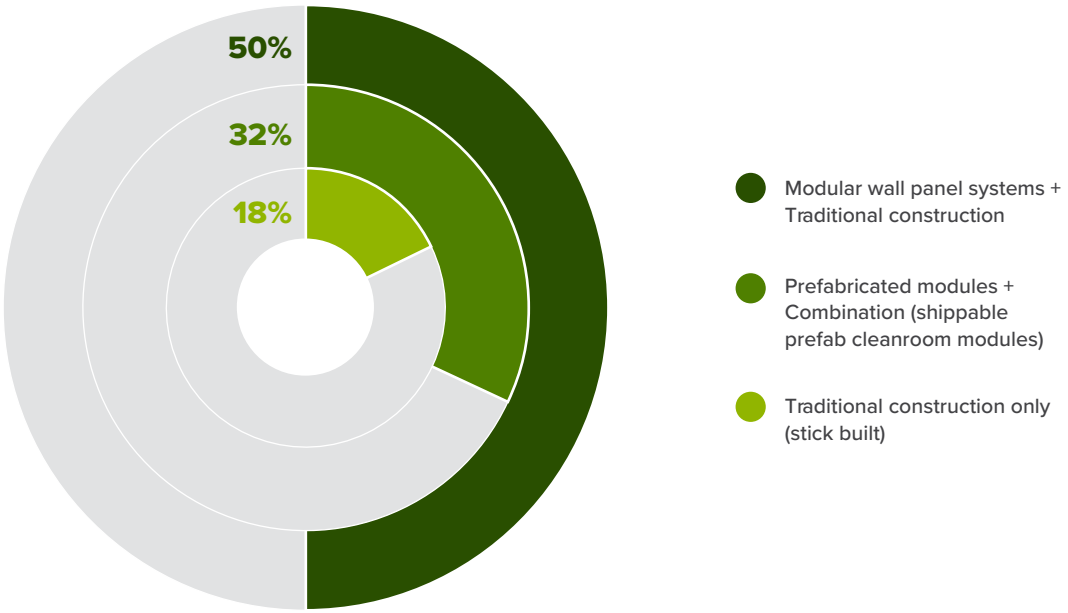
Standing on the precipice of revolutionary change and contemplating its advantages is one thing. Knowing how to prepare for it in real, everyday terms is another. ATMP startups that are new to therapeutic manufacturing might not be fully aware of the challenges they'll face as they move from the lab to the cleanroom. More mature companies with a history of dedicated, stick-built manufacturing sites and rigid procurement processes might have reservations about initiating a non-traditional capital development project.

For both types of companies and everyone in between, the first step in navigating this opportunity and unlocking its advantages is knowing which questions to ask. For example:

- **Scheduling and cost control:** How can you balance the pressure to get up and running as quickly as possible with the need to manage your costs, particularly while your products are in the early investigational stage?
- **Compliance and closed processing:** What will it take to ensure end-to-end regulatory approval when the concept of a multimodal facility is so new?
- **Partnership:** Should you invest in the necessary infrastructure to keep all your operations in-house, or find a CMO/CDMO to support some or all of your manufacturing and testing needs?
- **Supply chain:** Should you rely on a third-party supplier for your raw materials? What are the risks and potential payoffs of using your multimodal facility to manufacture plasmids, viral vectors and other necessary materials in-house?
- **Location:** Where should you put your multimodal facility? Near an urban center, where you're more likely to find top talent? Near a transport hub, which would simplify logistics? Next to a hospital or point-of-care facility?
- **Construction approach:** Traditional construction methods are falling out of favor as leaner, more flexible alternatives become available (Figure 8). What's the best option for your multimodal project? Should you take advantage of the speed of a prefab solution, despite its higher price tag? Or is the extremely popular approach of combining modular and stick-built systems best for your unique circumstances?

FIGURE 8

Q1: When executing capital expense projects, which model for cleanroom realization does your company favor? [Single Select]



Source: CRB

The next step, of course, is knowing where to turn for answers to these questions. A consultant with experience leading ATMP manufacturers into the multimodal revolution is one half of the solution; access to the right tools and insights is the other.

The magic happens when both halves come together, helping you design a successful multimodal facility based on strategic and methodical due diligence. This is often accomplished through detailed simulations, which allow consultants to demonstrate the impacts of potential real-world variables such as size, location, platform technology and supply chain strategy. Like a porthole that affords a glimpse of many potential futures, these simulations — and the experts who know when and how to make them count — can help you steer through these uncharted waters, ensuring you follow the best possible course towards the multimodal future that awaits.

MULTIMODAL 2.0: SUITE-LEVEL PRODUCT SWAPS

It may take time for our industry to accept the idea of segregated, side-by-side production under one roof, and we won't all reach that horizon at the same time. Early adopters will get there first and, once they do, they'll find another destination beckoning: multimodal manufacturing inside the same production suite.

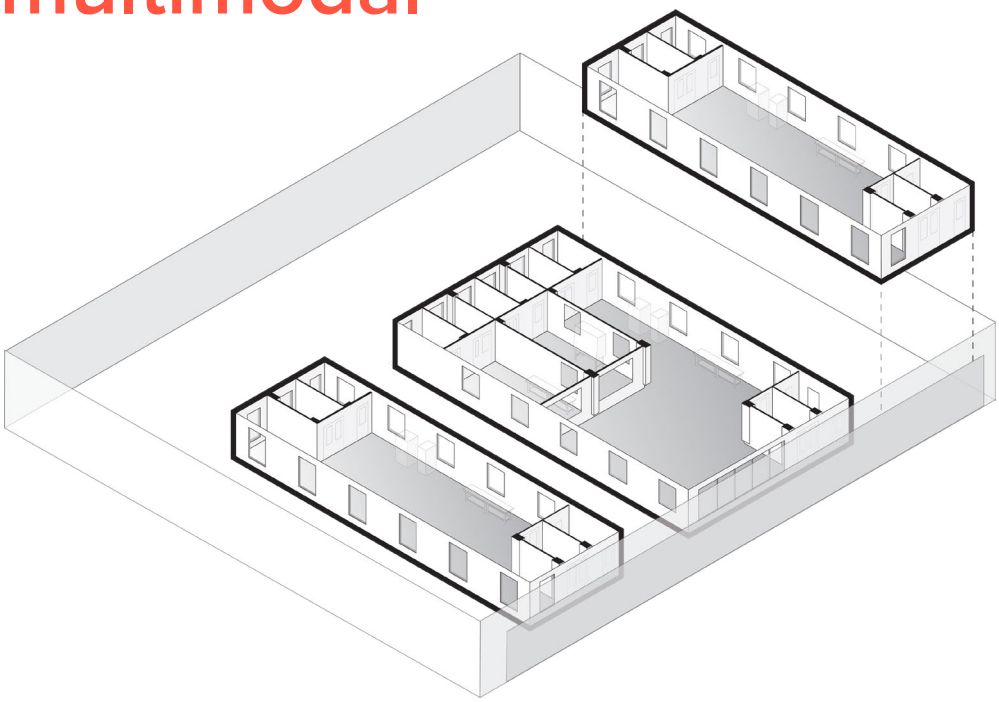
The idea is to identify products with operational and regulatory compatibilities and design a manufacturing environment that can campaign between them with minimal downtime. Manufacturers could use this model to develop intensely flexible and scalable spaces, designed for rapid decontamination and equipment turnover as

Companies could ready themselves for GMP manufacturing while their products are still in early development, confident that their investment will retain its value no matter which modality ultimately moves forward. The potential gains — both in terms of speed-to-market and ROI — are huge.

product pipelines change and expand. This gives new meaning to the idea of the future-proof facility; companies could ready themselves for GMP manufacturing while their products are still in early development, confident that their investment will retain its value no matter which modality ultimately moves forward. The potential gains — both in terms of speed-to-market and ROI — are huge.

Many will view this as a radical idea. Perhaps it is radical, but that doesn't mean it won't happen — and when it does, it will revolutionize biotech and ATMP manufacturing for a second time.

The momentum of multimodal



There's another dimension to Moore's Law that's less well-known. Alongside the dramatic growth of computer power, it predicts an equally dramatic decrease in its cost.

His prediction foretold a pattern that has repeated itself across industries ever since. A novel idea starts its life as relatively unattainable, whether because of its price tag, its complexity or its unfamiliarity (or all three). But if it's a good idea, if it solves the right problem in the right way, it will become more accessible (and accepted) until, eventually, it's ubiquitous.

Our own industry has many such examples. Think of the 1980s biotech explosion and the advent of the stainless-steel facility, or the arrival of closed processing technology many decades later, which brought with it the concept of a ballroom design. With each revolutionary idea, there's a period of uncomfortable adjustment. On the other side of that period: untapped potential.

10x

the usual speed

Multimodal manufacturing is following the same pattern but at 10 times the usual speed. ATMP manufacturers who want to own their future by taking control of their present have a narrow window right now to make their move — and it's a move that's sure to pay off for years to come.

Are Stable Producer Cells the Future of Viral Vector Manufacturing?

By: Peter Walters and Brita Salzmann

Viral vector manufacturing is on the verge of an extraordinary leap forward. Experts predict that the field will grow by as much as 20% per year over the next five years, driven by a surge in regulatory approvals for novel and in-demand cell and gene therapies.

20%

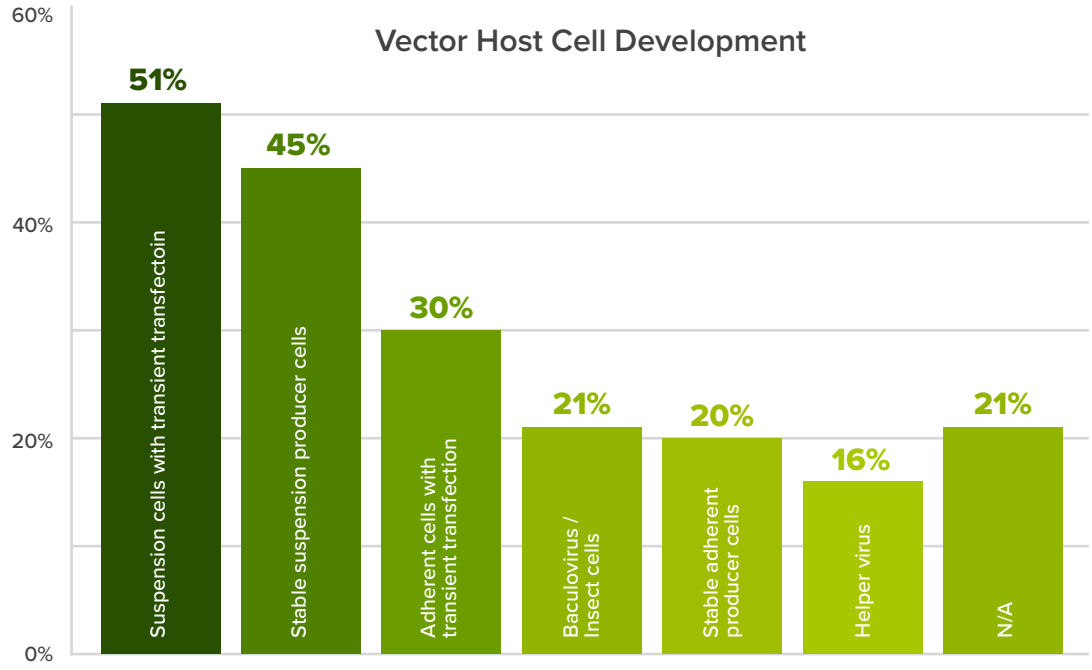
growth over the next five years

To climb such a steep growth curve, manufacturers must continuously push the status quo toward improved methodologies. This never-ending quest for change defines our industry — think of the shift from adherent to suspension-capable cell cultures, or from stainless steel to single-use technologies. Each of these revolutions opened a door to more efficient facility designs and much higher throughput, although walking through that door was not always easy without a period of experimentation, assessment and gradual acceptance.

We're at a similar inflection point today. While more than 80% of survey respondents rely on transient transfection to manufacture viral vectors from packaging cells (Figure 9), a new host cell line is gaining momentum: stable producer cells. A full 65% of survey respondents are developing (or intend to develop) this type of vector host cell, drawn by the potential for a less expensive, more scalable process. What this tells us is that stable producer cell lines, once considered the interesting aspiration of a small few, are here to stay, bringing with them an exciting new "norm" for viral vector manufacturers — and many new questions and challenges.

FIGURE 9

Q1: What types of vector host cells are you developing, or intend to develop, for viral vector manufacturing? [Select all that apply]



Source: CRB

NO HOLY GRAIL

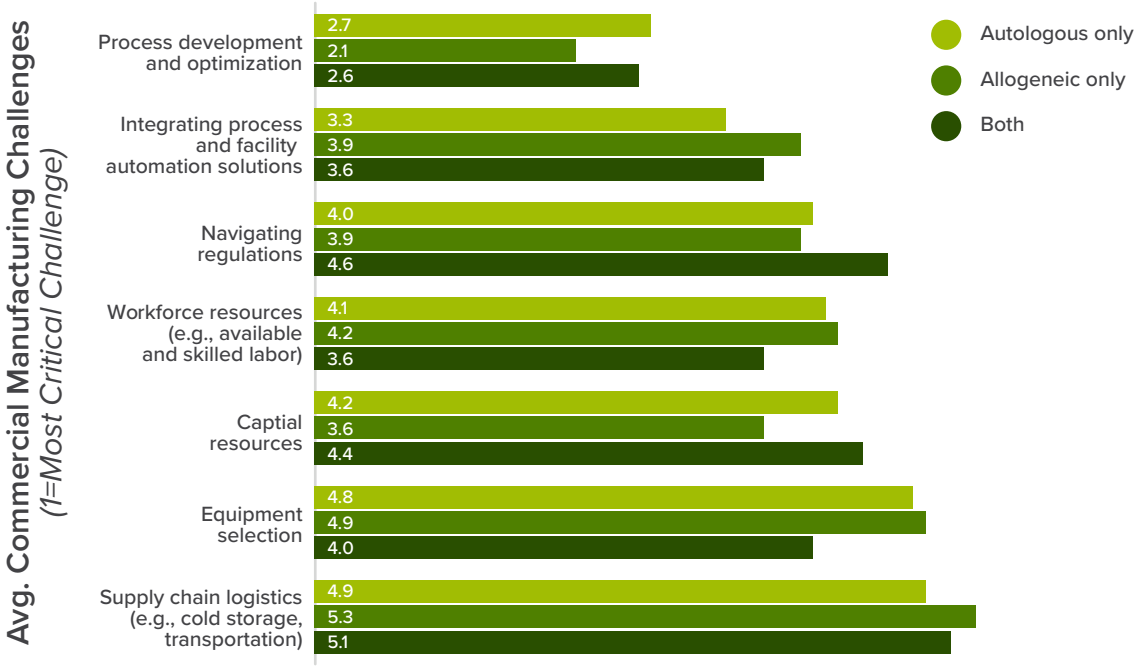
If you trace the excitement about stable producer cells to its original source, you'll find lab researchers rallying around a process that's far simpler than triple transfection and that frees manufacturers from the expense of sourcing plasmids and other transgene elements at full production scale from third-party suppliers. Their excitement is justified, but here's the catch: Each of those advantages conceals new challenges, particularly once manufacturers scale their stable producer cell process from the lab to the GMP cleanroom.

For example, manufacturers working with stable producer cells lose an ace up their sleeve because producer cells — unlike packaging cells — typically require end-to-end segregation. Instead of strategically managing their throughput by staggering growth cycles inside the same cell culture and production suites, manufacturers are at the mercy of two hardwired factors: the time required to grow a single batch of vector and the time required to turn over a production suite after that batch is complete. In other words, without proper planning, what may seem like an unstoppable magic bullet on a small scale can become a slow and awkward process at commercial volumes.

Given that the vast majority of our survey respondents are primarily concerned with process optimization (Figure 10), it's especially important that manufacturers think about this during early process development. How can they ensure that their producer cell manufacturing mode pays higher dividends than alternative processes across the whole manufacturing pipeline? The first step, of course, is understanding both the opportunity and its risks, and parlaying that understanding into a careful and well-considered plan.

FIGURE 10

Q1: What do you consider to be your biggest challenges in progressing toward commercial manufacturing? [Rank Order: 1=Most critical challenge—7=Least critical challenge]



Source: CRB

THE OPPORTUNITY: A SIMPLER PROCESS AND IMPROVED COST CONTROL

Stable producer cells remove complexity and improve reliability. First, let's consider traditional packaging host cells that are a necessary component of the triple transfection methodology. These cells are engineered to contain some of the genes necessary to propagate a specific vector. The transfection process begins once those cells grow to production volume, at which point manufacturers introduce plasmids or other transgene elements containing the missing genetic material necessary for the packaging cells to complete the viral vector formation. Once the vector components are expressed, those cells die off and the process must start again.

Triple transfection makes up what is arguably the most inefficient operation in the viral vector production lifecycle. Removing the need to transfect cells “at scale” would have a tremendous impact, which is exactly what manufacturers achieve with stable producer cells. These cells are transfected from day one, usually starting with the master cell stock itself. When they reach production volume, they already contain everything they need to generate vectors — no transfection necessary. The result is a simpler process with fewer operational steps.

Stable producer cells reduce raw material spending. Next to a simpler process, the other headlining advantage of this methodology is its potential for enormous savings. Because transgene conversion happens at the beginning of the producer cell growth cycle, manufacturers only need enough plasmid to transfect their initial cells. As those cells grow to production volume, the vector component genes and target transgene essentially grow with the cells, reducing the need for costly plasmids. This advantage may appeal to the survey respondents who identified budget as one of their top three manufacturing concerns (Figure 10).

To take advantage of these possibilities, manufacturers need to frame up their commercial-scale production processes right from their early research phase, ensuring that they move forward with a model that won’t limit their productivity as batch volumes grow.

Stable producer cells improve consistency. Because the triple transfection process requires plasmids and packaging cells to make contact and exchange material, it introduces the risk of variation between batches. Stable producer cells eliminate this process and the risk that goes with it, theoretically improving overall yield per batch as a result.

To take advantage of these possibilities, manufacturers need to frame up their commercial-scale production processes right from their early research phase, ensuring that they move forward with a model that won’t limit their productivity as batch volumes grow. To get that right, they need a nuanced understanding of the risk that stable producer cell methodologies introduce.

THE RISK: COMPLEXITIES AT THE COMMERCIAL SCALE (FOR NOW)

We’ve talked about the advantages of undertaking stable transfection at the start of the vector manufacturing process, thus creating stable producer cells that contain everything necessary to propagate a specific vector.

These advantages come with a tax, of sorts: Manufacturers face a much greater burden of responsibility when it comes to designing and proving the efficacy

and safety of their process, which can cost both time and money if they haven't anticipated this need.

To understand what we mean, consider that packaging cell cultures lack the genes to form a vector as well as the gene of interest until they expand to production volume. This means that for most of the vector manufacturing process, different cell batches can occupy the same suite and even — with strategic timing — the same equipment. Only once they're transfected do different cell cultures require segregation. Manufacturers can arrange their upstream cell expansion process to support the turnover time required for that last processing step. As a result, vector production using packaging cells is typically very efficient, yielding high throughput in relatively little time.

Stable producer cells, transfected from the outset and containing the gene of interest, don't offer that "efficiency advantage." To avoid cross-contamination, manufacturers may need to segregate each batch from the outset, which eliminates the opportunity to run concurrent batches in the same facility footprint. Instead, a single batch may tie up a cell culture and production suite for as long as it takes to run the full vector production lifecycle — or longer, because of the time required to turn that suite over before the next batch begins. This has an enormous potential impact on throughput at a commercial scale.

96%

of survey respondents use suspension cell cultures, which were once a new and disruptive idea

It's not inconceivable that manufacturers could achieve a throughput that's comparable with the triple transfection process. To get there, though, they would have to follow one of two challenging paths: either develop stable producer cell cultures capable of propagating a higher volume of vector per batch, or find a way to undertake multi-process manufacturing within their facility. The latter requires significant legwork, starting with a thorough risk assessment and followed by detailed studies and a costly process development exercise. Companies will need to plan ahead to follow either path to success.

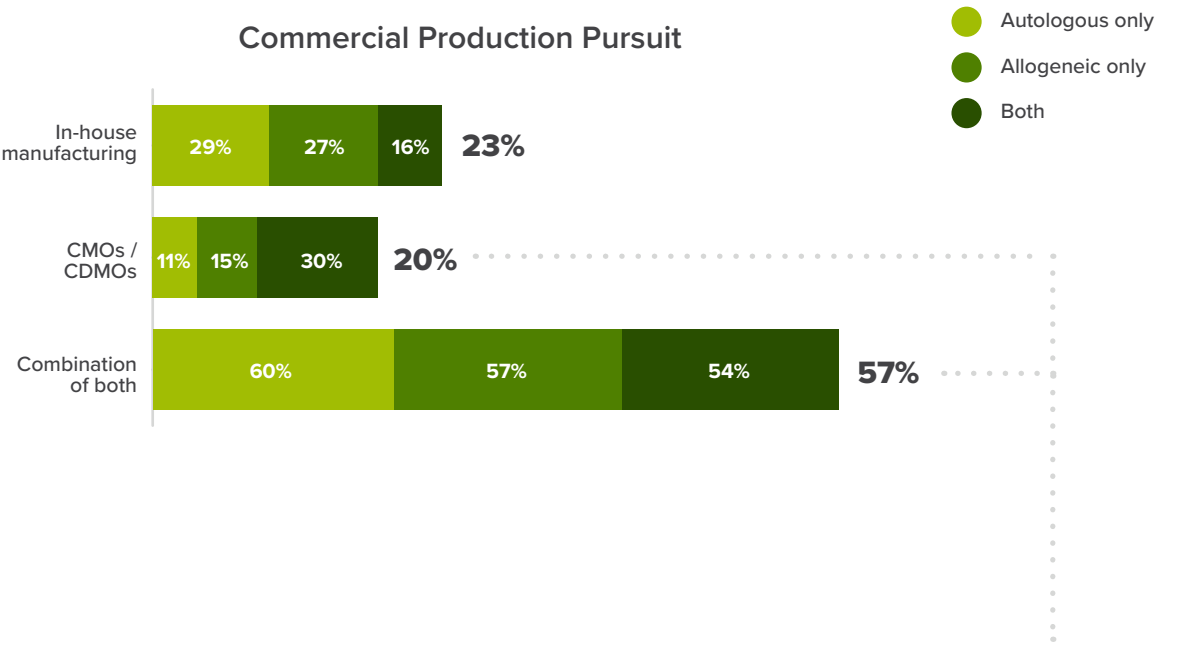
Viral vector manufacturers who are pursuing stable producer cells won't always face such a hard road. As these methodologies mature, the industry will find more efficient ways to align their output and cadence with individual facility use profiles. Again, we're following an evolutionary trajectory already sketched for us in the history of our industry; it's easy to forget that suspension cell cultures, in use by 96% of today's survey respondents, were once a new and disruptive idea that needed time and development to become the ubiquitous and cost-effective technology we now rely on. Over the coming years, stable producer cell methodologies are sure to follow suit.

SHOULD YOU CONSIDER PARTNERSHIP?

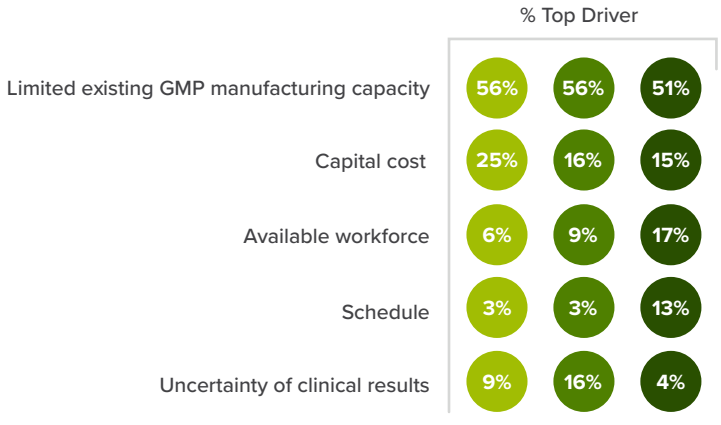
Until we're further along in that process evolution, many manufacturers are turning to a strategic partner for help. Nearly three-quarters of our survey respondents work with a CMO or CDMO in some capacity, most often as part of a hybrid in-house/ CMO model (Figure 11). This arrangement gives manufacturers an opportunity to own the development of their process without having to funnel huge capital sums into dedicated facilities and manufacturing talent. It also enables them to completely outsource specific components such as plasmid production.

FIGURE 11

Q1: In your progression toward commercial production, are you planning on pursuing: [Single Select]

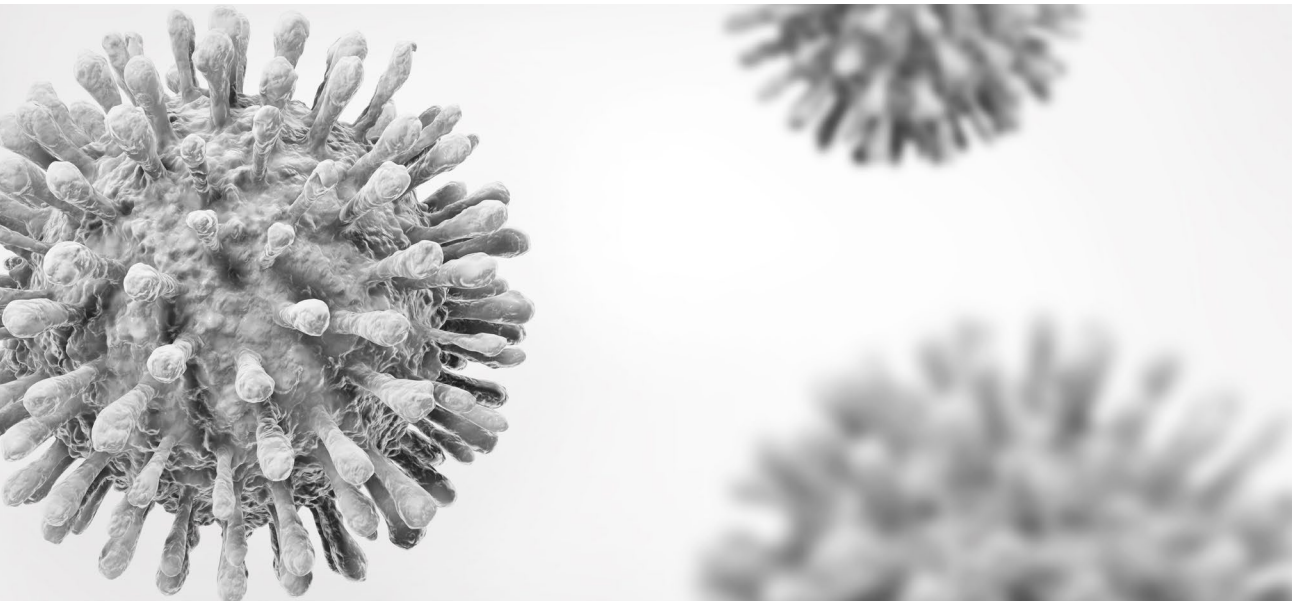


Q2: You indicated that you are planning on pursuing a CMO or CDMO as part of the manufacturing process. What are the drivers for that decision? [Rank Order: 1=Most influential driver—5=Least influential driver]



Source: CRB

Partnering does levy its own costs, though. Despite a recent surge in facility construction and expansion, it's not unusual for manufacturers to wait a year or more for an opening with a qualified CMO. This is likely a factor for the 27% of survey respondents who have chosen to pursue in-house viral vector manufacturing only. Rather than wait for the industry to catch up with demand, they're initiating their own solution and accepting the risks — and potential rewards — that come with going it alone.



Move forward with eyes open

Stable producer cell processes open the door to compelling new operational models that will shape the future of viral vector production. For example, what if manufacturers could propagate multiple batches of vector from a single stable producer cell culture? That would eclipse the productivity of the "terminal" triple transfection process and introduce all-new possibilities for the way manufacturers plan and qualify their facilities.

Just as it took time for our industry to understand and embrace historic revolutions in drug manufacturing, we don't yet know exactly how — and how soon — new approaches to viral vector manufacturing will impact facilities of the future. What we know for certain is that nothing will remain the same for long, and that our industry's innovators and pioneers will do what they've always done — find compelling solutions to the challenges that manufacturers face today so that they can continue to develop novel and life-sustaining genetic therapies for generations to come.

The Race is Won at the Start Line:
The Advantages of Early Facility Optimization

By: Dr. Niranjan Kulkarni and Brita Salzmann

Everyone wants an optimized facility, but there are few clear instructions for how to get it. That's especially true in ATMP manufacturing, where some of the industry's brightest minds are redefining how medicine can improve or save human lives, and yet few ATMP candidates have successfully reached commercialization. So much depends on the complex science of cell and gene therapy manufacturing, but just as much — or more, by some measures — depends on how well manufacturers translate that science into their facility and process design.

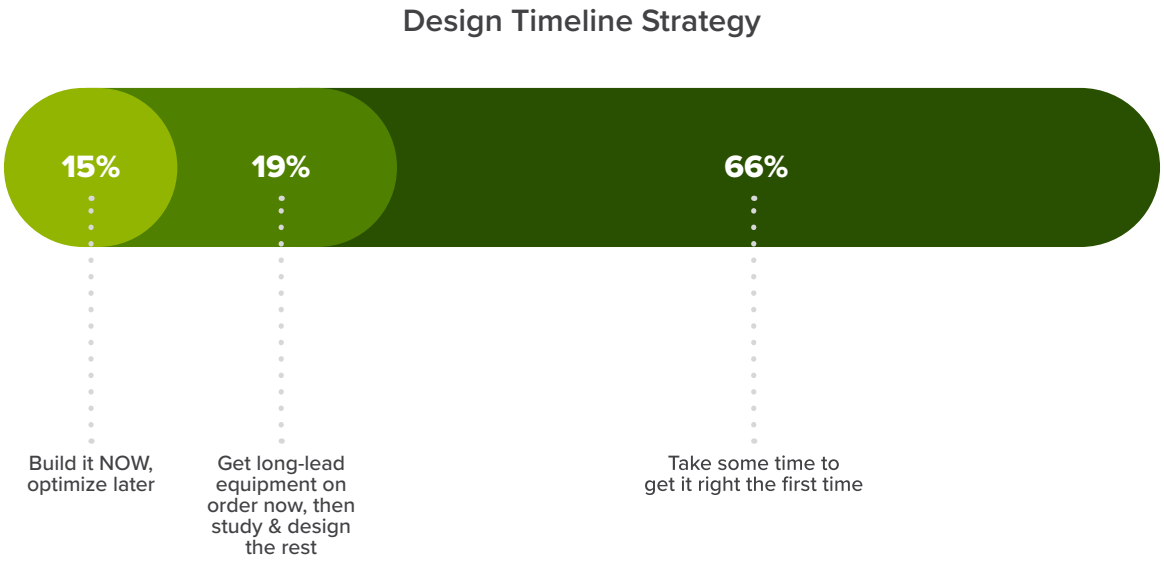
Optimization, always important, has now become mission critical.

Manufacturers know this. More than 77% of our survey respondents ranked process development and optimization among their top three commercial manufacturing challenges across both cell and gene therapy platforms. These manufacturers know something else, too: getting optimization right begins with the design of their new facility or product line from day one (Figure 12).

Optimization, always important, has now become mission critical.

FIGURE 12

Q1: What is your most likely design timeline strategy for a new facility or product line? [Single Select]



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All of this begs the question: When we talk about facility optimization, what are we talking about? What do ATMP manufacturers need to know about ensuring that their facility and their processes are as efficient, as reliable and as cost-effective as they can be?

INSIDE A FACILITY OPTIMIZATION EXERCISE

The "when" of optimization: the earlier you start, the higher your ROI

ATMP manufacturers face a minefield of unique and diverse risks. There's the risk of investing everything in a promising new therapy that doesn't succeed. If it does succeed, there's the risk of losing valuable time as nascent processes scale inefficiently from the lab to commercial production. And then there are the everyday, cumulative risks: gowning and segregation concerns, staffing challenges and threats to supply chain quality and security.

The "when" of optimization: the earlier you start, the higher your ROI.

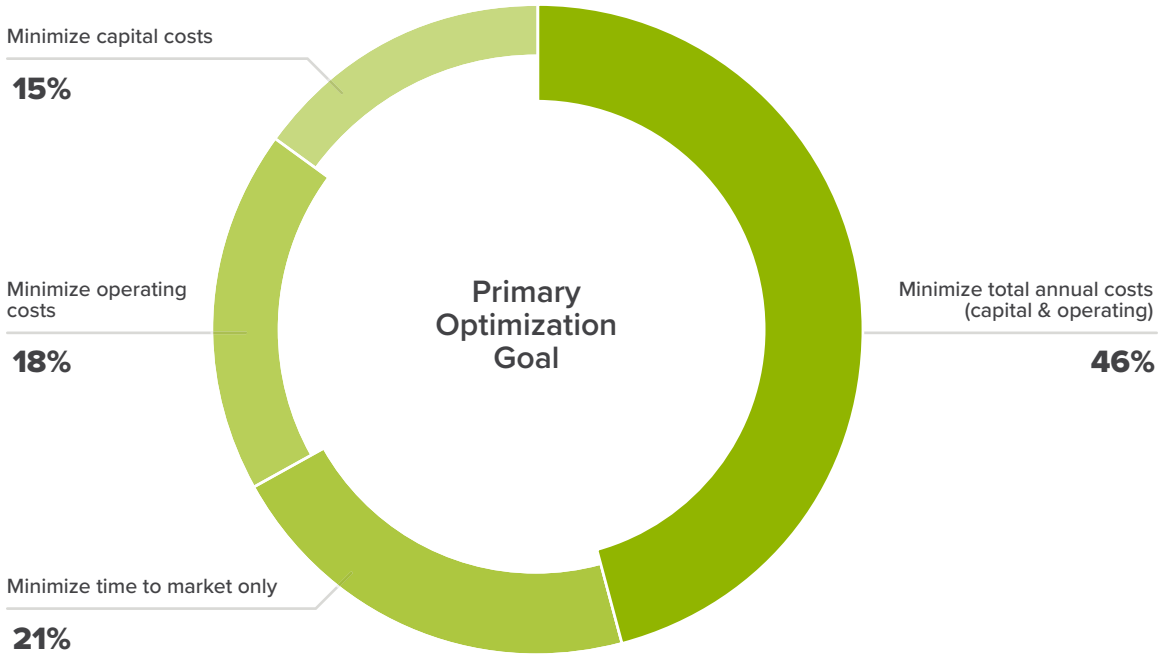
Manufacturers need a detailed map to guide them safely across that minefield. That's the big promise of optimization: it reveals the best possible path from high-level

conceptual planning to construction and, finally, to commercial operations. Defining this path from the beginning matters, because the further companies move along it, the more they'll pay — in budget and in lost time — to accommodate changes and resolve unexpected challenges.

There's also the progressively higher risk of making a mistake and undermining a design's synergy late in the project's development, leading to inefficiencies in construction and in the facility's ultimate performance. To avoid these roadblocks, manufacturers need to begin with the end in mind, using a facility optimization approach from day one. In this way, they'll avoid costly wrong turns and dead ends, ultimately delivering what nearly half of survey respondents consider their primary goal of optimization: lower capital and operational spending (Figure 13).

FIGURE 13

Q1: What is your primary optimization goal for a new or retrofit facility? [Single Select]



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The "what" of optimization: a safe place to study scenarios

That map we are describing, the one that helps manufacturers navigate risk and arrive at operational control and efficiency, is called a digital twin.

The digital twin is a specific and data-based environment that mirrors the real-

world facility down to its smallest parts, giving manufacturers a space for testing assumptions, running scenarios and fine-tuning strategies and processes before investing in real-world solutions.

From this seat of control, manufacturers can understand exactly how to resolve some of the key challenges they face: process predictability, supply chain resilience and readiness for future expansion/adaptation.

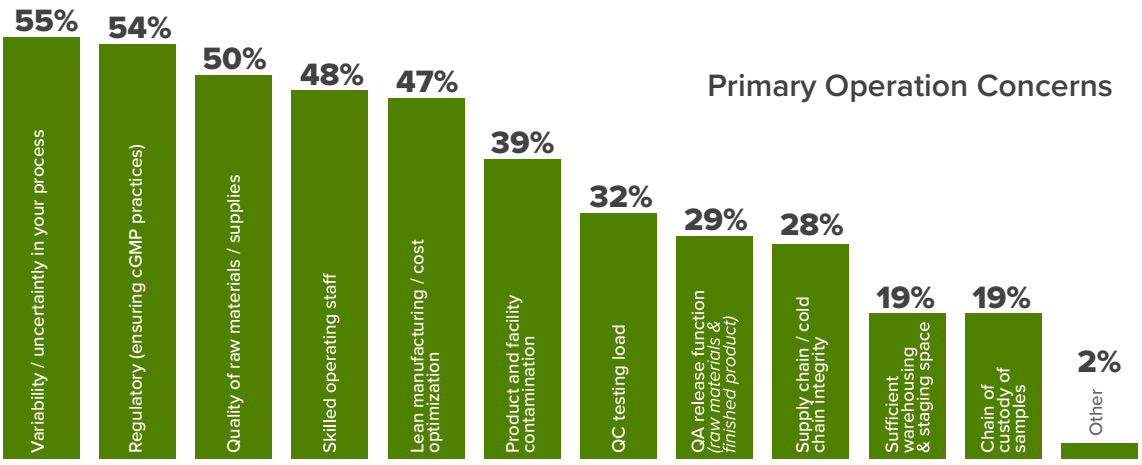
By feeding actual or estimates of operational data into the digital twin, manufacturers can run detailed simulations to understand the impact of just about every possible variable in their operations. It's like having a portal that can look backward, identifying and correcting chronic constraints or inefficiencies in an existing process, and forward, revealing potential future opportunities and risks based on multivariate inputs. From this seat of control, manufacturers can understand exactly how to resolve some of the key challenges they face: process predictability, supply chain resilience and readiness for future expansion/adaptation.

IMPROVE THE RELIABILITY OF YOUR PROCESS

The majority of survey respondents included variability/uncertainty in their process among their primary operations concerns, with regulatory considerations close behind (Figure 14). At the same time, more than a third feel concerned or anxious about their facility's achievable throughput.

FIGURE 14

Q1: What are your primary concerns with operations? [Select all that apply]



Source: CRB

The up-front work of facility optimization will address these concerns by laying the groundwork for a predictable and efficient manufacturing process, even — and especially — as that process transitions from the R&D lab to the cGMP cleanroom, where it's subject to regulatory scrutiny. By using the digital twin to map scenarios extending past current realities and reveal future constraints, opportunities, and risks, manufacturers can uncover concrete answers to some of their most urgent big-picture questions:

- How can we avoid costly changes as our project progresses from concept to construction without giving up the flexibility to evolve our design?
- How can we right-size our facility, including our manufacturing spaces, our warehouse and our QC labs, based on what we might need in the future?
- How can we ensure that a growing volume of personnel, consumables, waste and finished product flow through our facility efficiently and with no risks to human health or product quality?
- What process- or facility-related decisions do we need to make today to ensure ongoing regulatory compliance as we scale towards commercial production?

DESIGN RESILIENCY INTO YOUR SUPPLY CHAIN

As we write this article in the fall of 2020, our ATMP clients are navigating a turbulent period in the pharmaceutical supply chain. And while the immediate impacts of a global pandemic will someday fade, it's clear that turbulence of some degree — whether the result of geopolitical conflict, transportation failures or price fluctuations — is here to stay. We expect that's why more than a quarter of survey respondents placed supply chain/cold chain integrity among their top operations concerns (Figure 14), and nearly half report that their biggest supply chain worry has to do with raw materials (Figure 15).

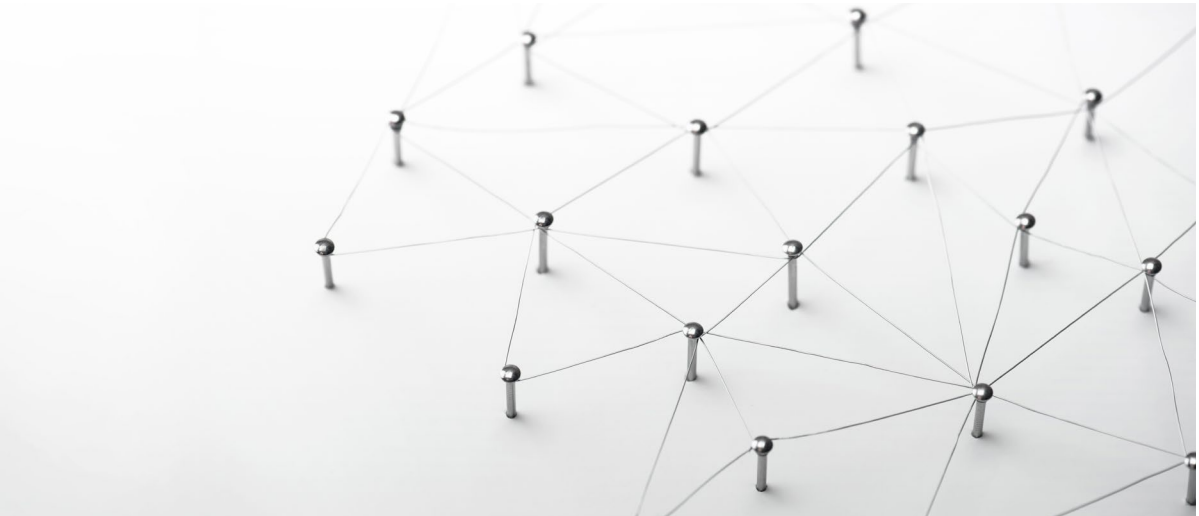
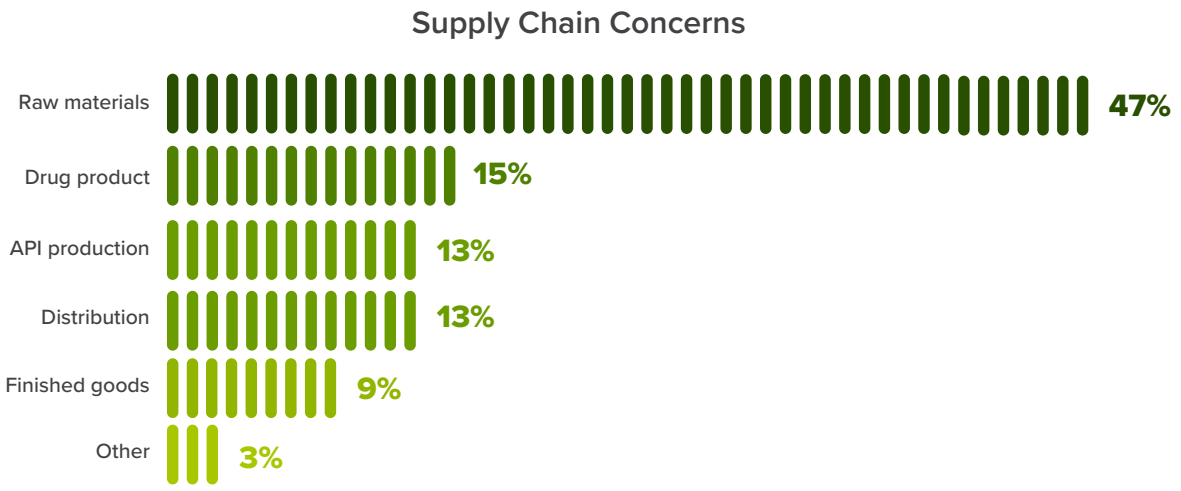


FIGURE 15

Q1: Which part of your supply chain concerns you most? [Single Select]



Source: CRB

In an optimized facility, these concerns are offset by the control afforded to manufacturers via their digital twin. We've already discussed how computer simulation can remove process-related bottlenecks and improve facility design; in the right hands, it's equally valuable in modeling events that impact supply chain and logistics planning. By undertaking various "stress tests" in a digital environment before facing those challenges when the stakes are high, manufacturers gain a dynamic and data-driven understanding of their supply chain's reliability. This gives them the insights they need to optimize their supply chain strategy, and to:

- Improve the lead times and traceability of materials across the manufacturing spectrum, from the needle to our facility and back to the needle.
- Calculate the amount of Material X or Ingredient Y to have in your safety stock, based on forecasted material lead times, pricing strategies material quality, etc.
- Quantify impact on the size and location of your storage capacity.
- Develop strategies to reduce the risk of materials falling out of specification during transportation.
- Assess risks in case key material is single sourced.

READY YOUR OPERATIONS FOR A FLEXIBLE FUTURE

We've seen how a data-based digital twin helps manufacturers see into the future and move safely through that minefield of risks we alluded to in the beginning. But there's another side to optimization, which has to do as much with seizing opportunities as it does with avoiding roadblocks.

Our survey respondents seem finely attuned to this. For example, more than half intend to adopt a multimodal manufacturing solution in two years or less, and 39% are strongly or very strongly committed to adopting the transformative, digital-first tenets of Pharma 4.0. One thing is certain: change is coming.

To satisfy this appetite for innovation and change, manufacturers need a tool that will help them confidently identify, assess and integrate the opportunities that are right for them, their patients and their business objectives, at the right time. That's where the digital twin can play a large role, indicating where an investment or a change in direction is likeliest to pay off and answering such elusive questions as:

- How can our facility embrace the flexibility of a multimodal platform, while designing out its risks and uncertainties?
- How can we improve the reliability of our equipment and our digital systems by adopting new technologies and taking advantage of intelligent automation?
- How can we respond quickly to the shifting dynamics of our market and the evolving needs of patients?

To optimize, opt in from day one

The unique challenges and opportunities of the ATMP field mean that manufacturers are especially well-positioned to benefit from optimization, particularly when it's braided into process and facility design from the start.

Before making far-reaching decisions that will be hard (and expensive) to reverse, manufacturers can rely on the tools of optimization — particularly the digital twin, modeled on the real and theoretical dynamics of the production environment — to swap guesswork for certainty and ensure that every step forward is a step towards a flexible, scalable, efficient and high-quality commercial manufacturing operation.

How ATMP Manufacturing Will Shape the Future of Project Delivery

By: J. Lee Emel

Speed. Cost control. Quality.

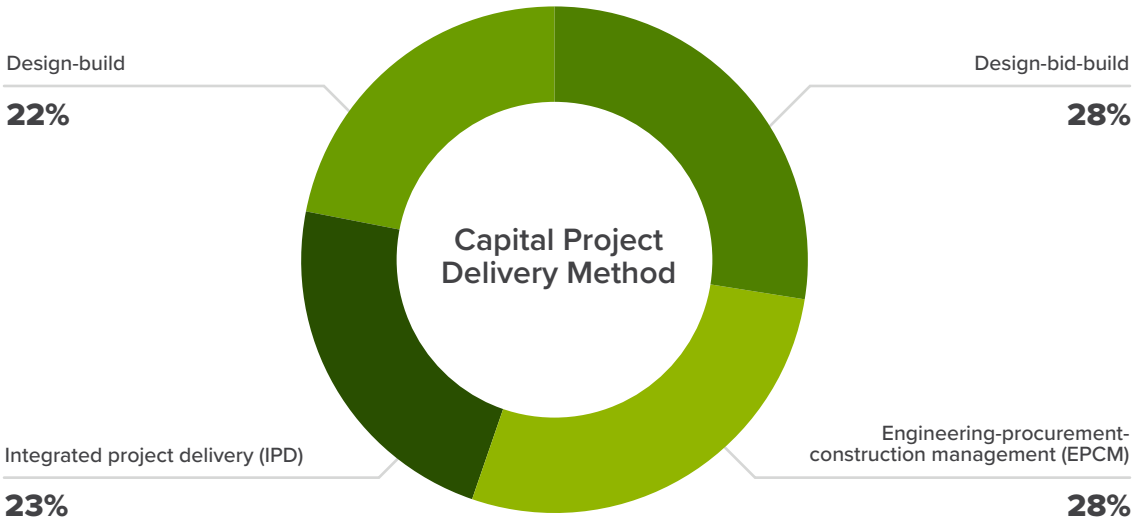
Pick two:			
	● Speed	● Cost Control	○ Quality
	● Speed	○ Cost Control	● Quality
	○ Speed	● Cost Control	● Quality

If you've been part of a traditional design-bid-build (DBB) project in the past, chances are you know what's next: *sacrifice*. Because you only get two. Want your project delivered on-time and on-budget? Fine, but its quality may suffer. Can't live with that? You can have quality — but only if you pay more or kiss your scheduling targets farewell.

This impractical choice has persisted for as long as traditional project delivery has been around, which is to say a long time — and it hasn't aged well. That's why we find our survey data encouraging. Not long ago, 100% of respondents would have been using DBB. Today, that number has fallen to just 28%, while the rest search for more integrative alternatives (Figure 16).

FIGURE 16

Q1: What capital project delivery method do you currently use? [Single Select]



Source: CRB

Over the next few years, ATMP manufacturers will continue to propel our industry into a promising era of holistic project delivery, one that embraces three key ingredients of successful execution: ***the right people, the right team culture and the right delivery methods.***

We're not surprised to see ATMP manufacturers leading this overall migration towards modern and more efficient project delivery methods. A desire to improve upon the status quo is coded into their DNA. They've already moved the goalposts in pharmaceutical manufacturing, and now they're accelerating the adoption of the non-traditional project delivery methods that make those manufacturing goals achievable. Over the next few years, ATMP manufacturers will continue to propel our industry into a promising era of holistic project delivery, one that embraces three key ingredients of successful execution: the right people, the right team culture and the right delivery methods.

CHOOSE YOUR PEOPLE FIRST

Discussions about project delivery often focus on tools and methodologies, leaving out what is arguably the most important success factor: the people involved.

Thinking about who you're hiring is antithetical to the lowest bidder philosophy that dominates DBB projects, which initially seems to be fiscally responsible — but has the same karmic effect as cheating on an exam: the consequences will find you in the end and will cost you more.

Instead, forward-thinking capital project owners in the ATMP space are searching for partners whose attraction is their experience and industry-specific knowledge, not (only) their cost. These are the experts whose combined skills will help ATMP manufacturers design and build facilities that are so much more than a cleanroom with equipment inside — facilities that answer their most pressing questions:

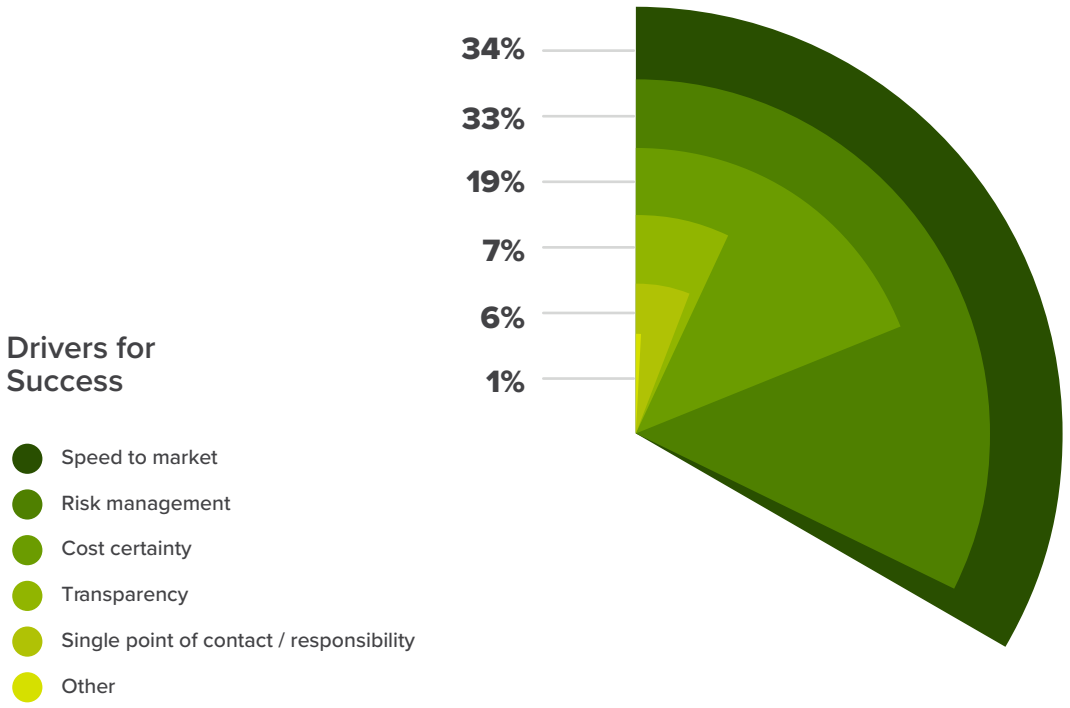
- How do I prepare for the twists and turns of a fast-moving and unknown future?
- What if my platform or my molecule changes? Will I still have a useful facility?
- How do I plan for commercial-scale production while I'm working with small volumes in my lab?

This shift in priorities, from cost to expertise, will challenge startups and big pharma companies in different ways. Startups are likely free from the baggage of a capital project legacy. While this means they may be open to novel approaches, it also means they're vulnerable to influence. Without the experience to decide for themselves, they may be directed into a project delivery mode that suits the whims of a particular consultant rather than one that suits the unique nature of their project. To reach the best possible outcome, these companies must educate themselves and choose a partner capable of moving in a new direction.

More mature companies may face a different kind of hurdle. They have the advantage of experience, but that could make it harder for them to depart from the well-worn methodologies of the past in pursuit of the leaner, faster, more agile approaches of the future. This may change as pressure mounts to reach the market first without taking on too much risk, all while managing costs (Figure 17). Patience is running out for traditional methodologies that don't make room for all three of those drivers.

FIGURE 17

Q: What would be your drivers for success? [Single Select]



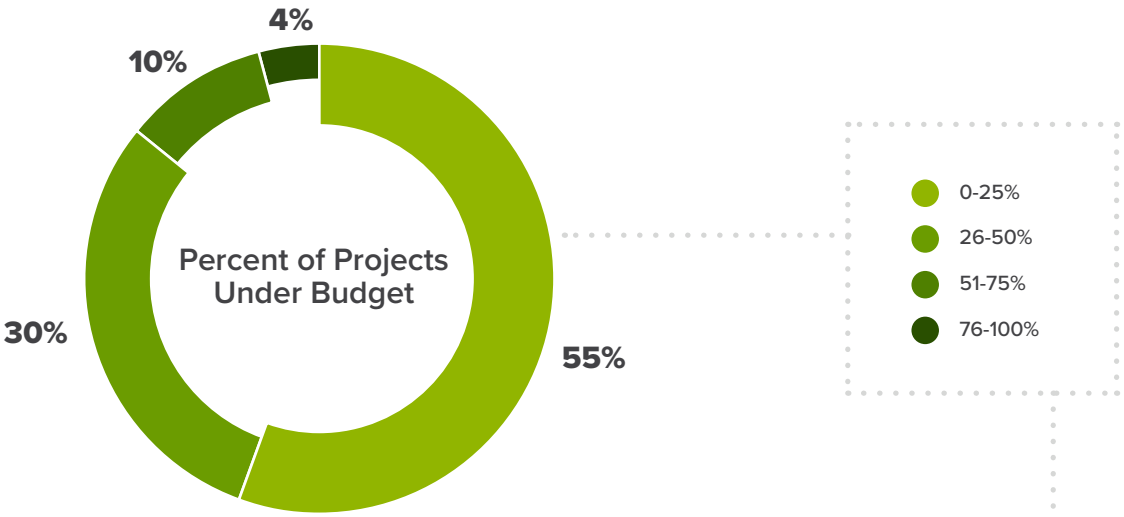
Source: CRB

INVEST IN A CULTURE OF TRUST

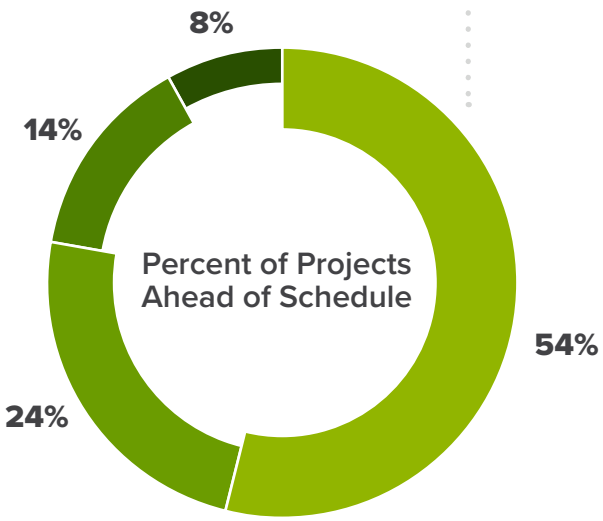
Finding the right combination of expertise is a good first step, but it's not a guarantee of successful project outcomes. Just look at how respondents reacted when our survey asked them to rate their highest-performing projects (Figure 18).

FIGURE 18

Q1: Based on your highest performing projects over the last five years, please estimate in percentages how many came under budget? [Single Select]



Q2: Based on highest performing projects over the last five years, please estimate in percentages how many were completed on or ahead of schedule? [Single Select]



Source: CRB

We're certain that these project teams included qualified and experienced people, yet on average only about a third finished under-budget and on-time. People are part of the solution, but owners need to empower those people with the right working environment if they want to improve their project outcomes, particularly when it comes to the novel facility solutions required for agile ATMP manufacturing. They need to build trust between all stakeholders, from designers and construction leaders to suppliers and subcontractors.

It's not as though proponents of traditional project delivery methods don't agree that trust matters. In fact, some could argue that DBB got its start because project owners needed a system they could trust, controlled by rigorous checks and balances meant to minimize risk. But what if we approached project delivery from the opposite angle? Instead of putting our trust in a system, what if we put our trust in people? What if we focused on maximizing opportunities for collaboration rather than on minimizing risks? From witnessing the results first-hand, we have a pretty good idea of what happens: Individual priorities give way to shared goals, and shared goals create happier, more synchronous teams. Happier teams mean greater productivity, faster, more effective problem-solving and better results from every angle — speed, cost, safety, scalability and flexibility.

This is a slippery concept. Dollars and deadlines are easy to measure, but trust? And if you can't measure it, how do you know when it's there, and if it's working?

You *can* measure it. Take requests for information (RFIs). It's not unusual for traditional, large-scale construction projects to accumulate hundreds of RFIs, each one funneling time and attention away from the project itself. That changes when subcontractors work alongside designers and construction experts from day one. Under those conditions, everyone understands how their daily efforts impact those downstream of their activities. There are fewer wasteful activities, many opportunities for direct and open communication across all parties and, in most cases, RFIs disappear altogether. That's just one example of the measurable difference that a positive and trusting culture can make.

When you partner with the right experts and establish a culture of trust and shared accountability, you're not only able to improve your speed and cost control — you're also much better positioned to take advantage of non-traditional solutions, like the turnkey approach to project delivery.

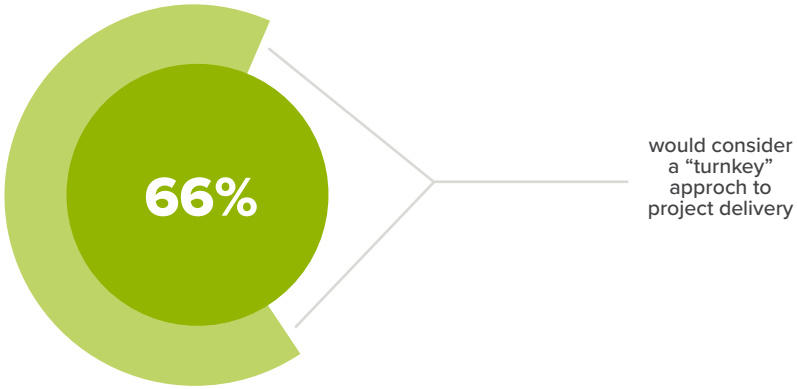
THE TURNKEY APPROACH

When you partner with the right experts and establish a culture of trust and shared accountability, you're not only able to improve your speed and cost control — you're also much better positioned to take advantage of non-traditional solutions, like the turnkey approach to project delivery.

The majority of our survey respondents say they would consider turnkey for their next project (Figure 19), and we expect this trend to rise dramatically over the coming years.

FIGURE 19

Q1: For your upcoming projects, would you consider a "turnkey" approach to project delivery, a method that is end to end, from design and construction through start-up and operator training? [Single Select]



Source: CRB

Not everyone is ready for this evolution. More than a third of our survey respondents say they would not consider a turnkey approach, and they gave some fascinating reasons why:

Turnkey Detractors

"Communication and project control by key stakeholders is lost."

"Prefer to control project development in-house."

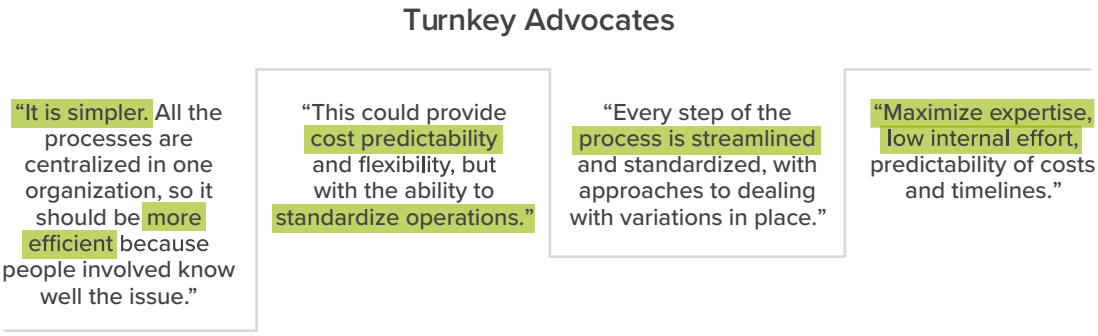
"We desire to remain nimble and 'turnkey' often takes away flexibility."

"Ties company to single option, multiple sources and flexibility is important."

The anxiety is understandable. If you're a project owner who's used to playing the middleman between compartmentalized entities on DBB projects, your perception of what's required to keep moving forward is tied up in maintaining control and keeping your options open.

Interestingly, survey respondents in favor of turnkey are as passionate about maintaining flexibility as those opposed to it. Instead of seeing a loss of control, though, they see an opportunity to accelerate project delivery by trusting industry experts who can help them meet their objectives.

A turnkey facility, stewarded by a project team that understands your objectives and knows how to get you there by balancing standardized design with customization, provides exactly what its detractors fear giving up: flexibility and control, as well as simplicity, speed and predictability.

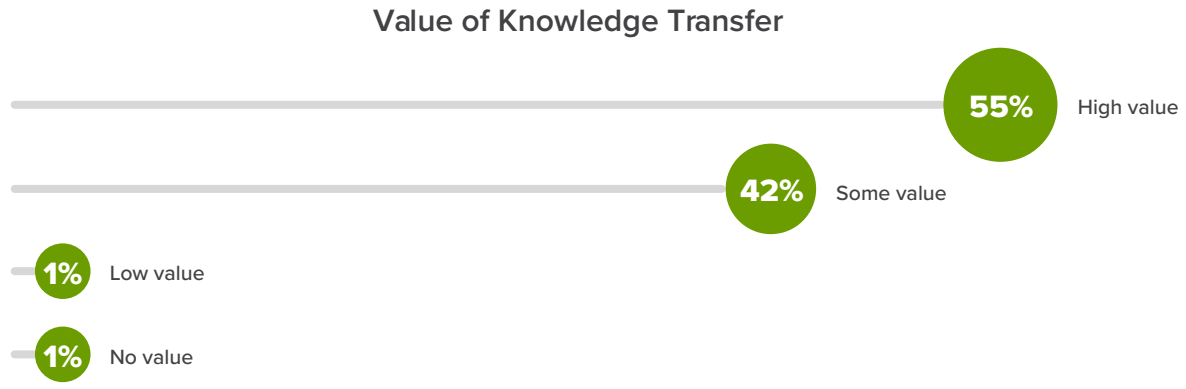


Importantly, turnkey projects don't stop delivering once the ribbon is cut. Part of their end-to-end promise is about providing continuous support and training, ensuring that manufacturers get the most from their new asset. As 97% of our survey respondents demonstrated, this commitment to knowledge transfer is valuable, particularly for those transitioning from the lab to the cleanroom for the first time (Figure 20).

ATMP manufacturers want results. They don't want to spend their time refereeing conflicts between project entities; they want the simplest and most cost-effective path towards a flexible, robust, validation-ready facility. And they want a partner who will help them understand how to use that facility to its fullest potential. A turnkey approach, which covers everything from design and construction through start-up and operator training, is the way forward, and we expect to see a boom in this delivery approach over the coming years.

FIGURE 20

Q1: How much would you value knowledge transfer to your team (facility operations/ limitations, process and equipment intent and operation, etc.) as part of the project delivery approach? [Single Select]



Source: CRB

The future of project delivery

Today's ATMP manufacturers are focused on developing transformative cell and gene therapies, and they expect equally transformative project delivery methods that solve the complexities of this brave new world.

They don't want to be backed into a choice between speed, cost control and quality. They expect all three and more — scalability, flexibility and expertise. And because ATMP manufacturers are by nature an enterprising and innovative force, they'll invent a way to get it. They'll bring together the right people, they'll invest in a culture of trust and shared ownership and they'll push for smart and nontraditional approaches to capital project delivery.

This is their future, and it's about to change everything.

Adopting a Regulatory Mindset for the Making of ATMPs

By: Marc Pelletier

The ATMP field is defined by its rapid progress, whether in terms of scientific discovery, product development or evolving and expanding therapeutic applications. These changes have almost always moved faster than regulation.

In some cases, regulators are familiar with ATMP technologies and unit operations, which are borrowed from the well-established field of monoclonal antibodies; in other cases, though, the emerging technologies and process platforms for ATMP production are not (yet) compatible with GMP regulations. Making a wrong decision — or a decision that works for small-batch production but will not scale to commercial-volume GMP production — could result in significant regulatory delays. With so much depending on speed-to-market, avoiding these risks is paramount.

ATMP manufacturers need a regulatory strategy to guide them from the outset of development, ensuring that the decisions they make as they scale their production help them maintain uninterrupted compliance.

That's why ATMP manufacturers need a regulatory strategy to guide them from the outset of development, ensuring that the decisions they make as they scale their production — or as they partner with a CMO for that purpose — help them maintain

uninterrupted compliance. With a strong understanding of ATMP regulations in place from the start, manufacturers can maximize and optimize their facility and process design, and they can engage with the government as a full partner rather than a hindrance.

What does it take to get there? What are the critical elements that manufacturers need to know and do to continue their promising work safely and in compliance with the latest regulations?

REGULATIONS ARE HARMONIZED GLOBALLY WITH SOME COUNTRY-SPECIFIC DIFFERENCES

Manufacturers of ATMPs must adhere to regulations that apply to medicines given intravenously. Most of those surveyed (78%) are making products destined for human or veterinary use. The European guidance documents don't distinguish between products for human or veterinary use, while the FDA has separate regulations for each.

50%

of survey respondents distribute their products worldwide

Drugmakers have to follow the regulations in the jurisdictions in which they intend to distribute their products. While 43% of respondents make ATMPs for the U.S. and 28% for European markets, half of them distribute their products worldwide, making an understanding of global regulations imperative.

Given that each country has its own regulatory body overseeing manufacturing compliance, having harmonized guidelines has been a boon for companies that operate in multiple jurisdictions. To this end, the Pharmaceutical Inspection Co-operation Scheme (PIC/S) — a network of 53 regulatory authorities responsible for the GMP of medicinal products for human and veterinary use — functions to harmonize inspection practices and GMP standards worldwide. PIC/S represents as much as 95% of the countries in which ATMPs are distributed and each of its inspections includes representatives from five countries other than the one in which an ATMP is made.

BIOSAFETY REGULATION GUIDELINES

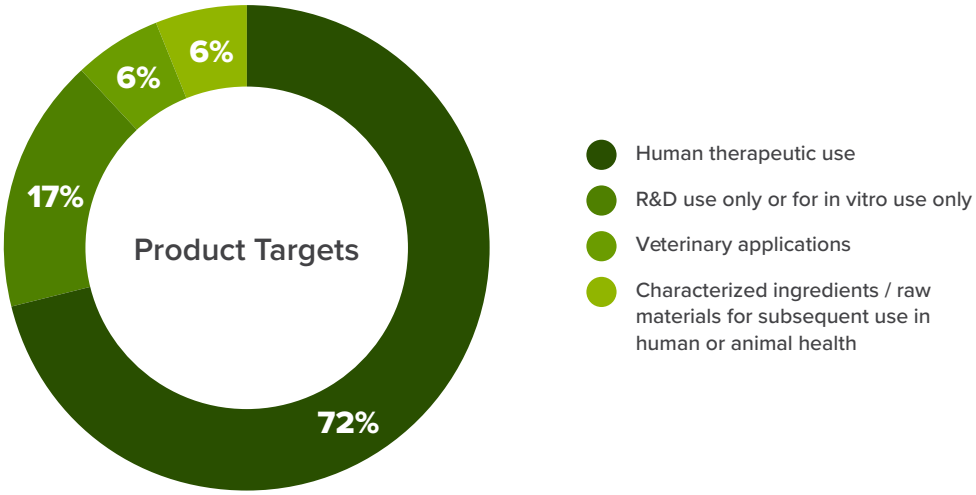
Biosafety considerations include safeguarding human health as well as protecting the process from contamination that could jeopardize production.

Some viral vectors are infectious, a potential hazard to humans, and require biosafety level (BSL) 2 or higher. In terms of biosafety when using human cells, the regulations tend to be more stringent in the U.S. because the FDA categorizes human cells, which are the foundation of ATMP manufacturing, as a BSL 2 hazard. In Europe, human cells are a risk category 1, and sometimes, because the subsequent containment requirements are lower, manufacturing ATMPs in Europe will make more sense.

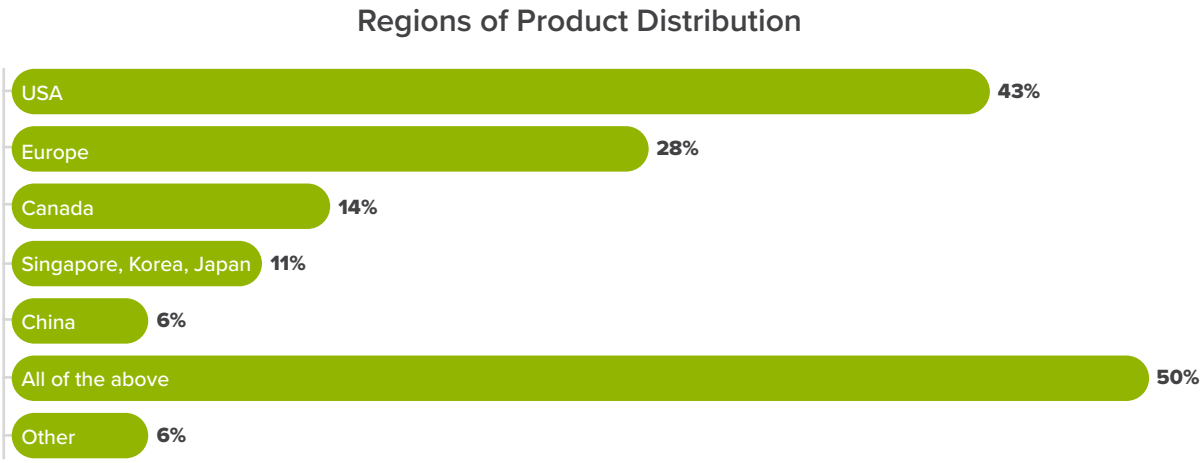
Host cells also need to be protected from contamination. Take baculovirus, which is used to make recombinant proteins in insect cells and as a delivery vector for modified genes. The host insect cells have to be protected from human or other contamination, which can be a concern for flu vaccine manufacturers that use baculovirus as a vector.

FIGURE 21

Q1: Is your company manufacturing products for? [Single Select]



Q2: Will products be distributed and used in...? Please select all that apply. [Multi-Select]



Source: CRB

THERE IS CONSENSUS AMONG REGULATORS AND AGENCIES ABOUT WHICH GUIDELINES ARE MOST IMPORTANT TO FOLLOW

Respondents said they comply with the most important regulatory guidance documents in Europe and the U.S. In Europe, respondents say they're complying with Part 4 of Eudralex, a summary document that is considered the best current guidance document on the production of ATMPs.

In the U.S., the FDA has created a series of white papers that line up fairly well with Part 4 of Eudralex, and respondents indicated they're in line with the most relevant guidelines for "Chemistry, Manufacturing and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (IND) Draft Guidance for Industry", particularly 21 CFR 312.23, 21 CFR 1271, 21 CFR 210, and 21 CFR 211.

With the ATMP standards enshrined in the Eudralex, there is a mechanism by which manufacturers can truly evaluate and design their cell processing systems in the correct environments, including the use of closed processing.

Regulators recommend closed processing whenever possible to reduce patient risk.

In 2013, the International Society of Pharmaceutical Engineers (ISPE) published Baseline Guide Vol 6: Biopharmaceutical Manufacturing Facilities (2nd Edition), which gave a snapshot of where the industry was headed. This is where we introduced the concept of closed bioprocessing, laying out the rationale and criteria for what is closed and what is not. Soon after, regulators began recommending the use of closed bioprocessing whenever possible because they saw that it constituted the safest way to make biologics with the least risk of contamination, including for vaccines, mAbs and ATMPs.

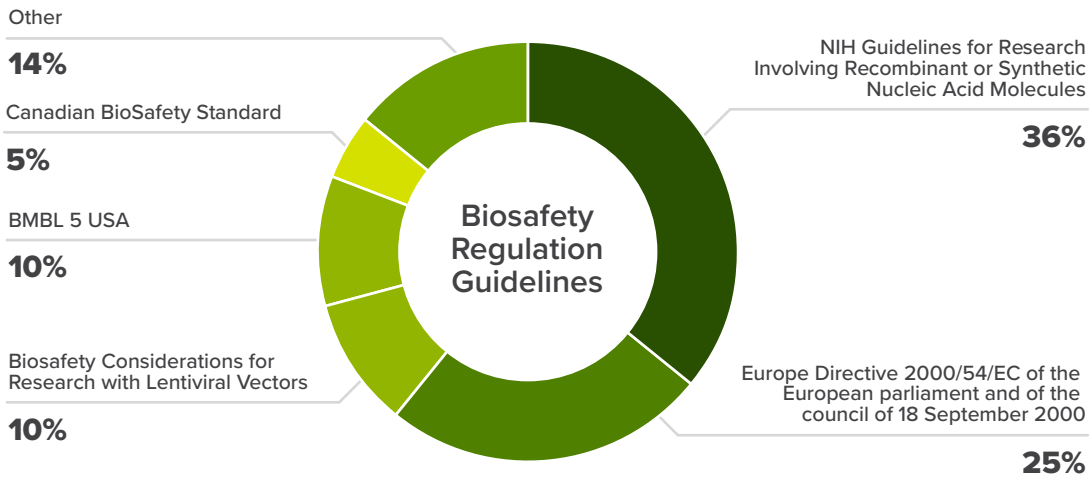
There wasn't an immediate evolution in facility design. Manufacturers continued to use legacy strategies for facility design and overall operations, such as adding ultra-cleanrooms when it wasn't necessary. ATMP production — still small scale and using new technologies — hadn't been designed for human therapeutic use and companies weren't validating that their processing systems were closed.

Closed processing has significant benefits.

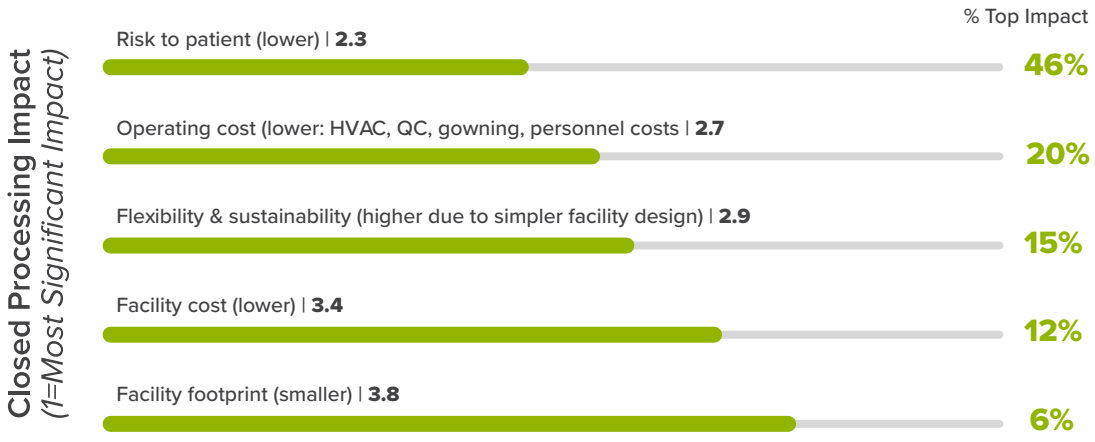
In 2018, the new European regulatory guidelines reiterated the importance of closed bioprocessing and stipulated that, whenever a process could be contained or closed, it did not require a cleanroom and could even be placed outdoors. The Eudralex and the FDA guidance documents spell out how to comply, and soon, every other regulatory agency will be promoting the need for closed processing.

FIGURE 22

Q1: Assuming your ATMP manufacturing scheme will use a human cell line, which biosafety regulatory guidelines does your company comply with? [Single Select]



Q2: Regulators have emphasized the use of closed bioprocess systems where possible. Although equipment cost can be much higher, closed processing can significantly impact: [Rank Order: 1=Most significant—5=Least significant]



Source: CRB

PIC/S has specific guidelines for ATMP production that closely reflect the Eudralex with only a few subtle differences. Consultants no longer have to fight to convince their clients to use either a closed system or isolators in place of an ultraclean BSC. If they place part of their process in a BSC, they must house it in an ultra-cleanroom, which is expensive.

Closed processing has significant benefits, as indicated by respondents:

- **Lower risk to patients** was identified by almost half as the top impact. We work with a North American client that, in the quality policy document for its new plant, made the statement that its plant would be based on closed processing. The FDA questioned this, not liking the idea of people coming to work in blue jeans and not wearing gloves. The company's second statement answered this concern, stating that it was using closed processing because *it represents a lower risk to patients*. That's a powerful statement. We've validated this strategy and recommend closing the process because it represents the lowest risk option for adulteration of a drug.

  We often use a simple metaphor to explain this. If one has a bottle with a cap on it, it doesn't matter where that bottle is stored as long as the surface is wiped before the cap is opened. You could drink out of that bottle even if it's been sitting in a basement for two years.

costs should decrease

25-40%

when downgrading from Grade C to a Grade D cleanroom

- **Lower operating costs** are possible because, as the need for protecting the environment from contamination goes down, gowning is decreased, HVAC needs are lower (instead of 30 air changes/hour, it's now 6), there are no airlocks and there's much less environmental monitoring by quality control. Costs should decrease between 25–40% when downgrading from a Grade C to a Grade D cleanroom.

$500M vs. $150M

- **Flexibility and sustainability** are enhanced because a facility can be designed using a concept similar to a convention center. The Javits Center, a convention center in New York City, has been used for auto shows, as a temporary hospital during COVID-19, for INTERPHEX, and 50 other events, all in one year. They can do this because it's an open space. An ATMP manufacturing facility without solid interior walls, airlocks and the need for gowning is flexible enough to be used for fill-finish one day, monoclonals soon after and then for ATMPs. Bespoke plants, designed for making one biologic, can cost upwards of $500,000,000 to build. Such a plant could be built, using closed processing, for $150,000,000 and, if the manufacturer wanted to make a different product, it could be converted in less than a year.

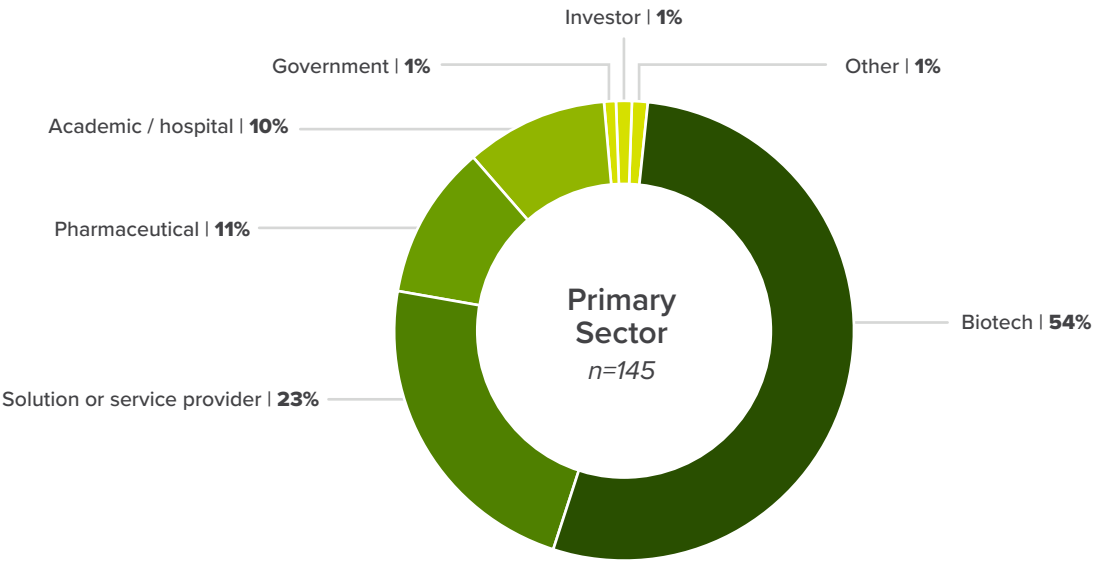
- **Facility costs are lower** because cleanrooms are downgraded. A heavily siloed facility costs more than $4,000 per square foot. A Grade B cleanroom can cost up to $3,500 per square foot (for the cleanroom alone). Compare this to less than $1,000 per square foot for a Grade D cleanroom.
- **The footprint can be smaller** considering that 12–25% of the floorspace of a heavily siloed facility consists of corridors and airlocks. A Grade D facility eliminates both, reducing the footprint of the manufacturing area.

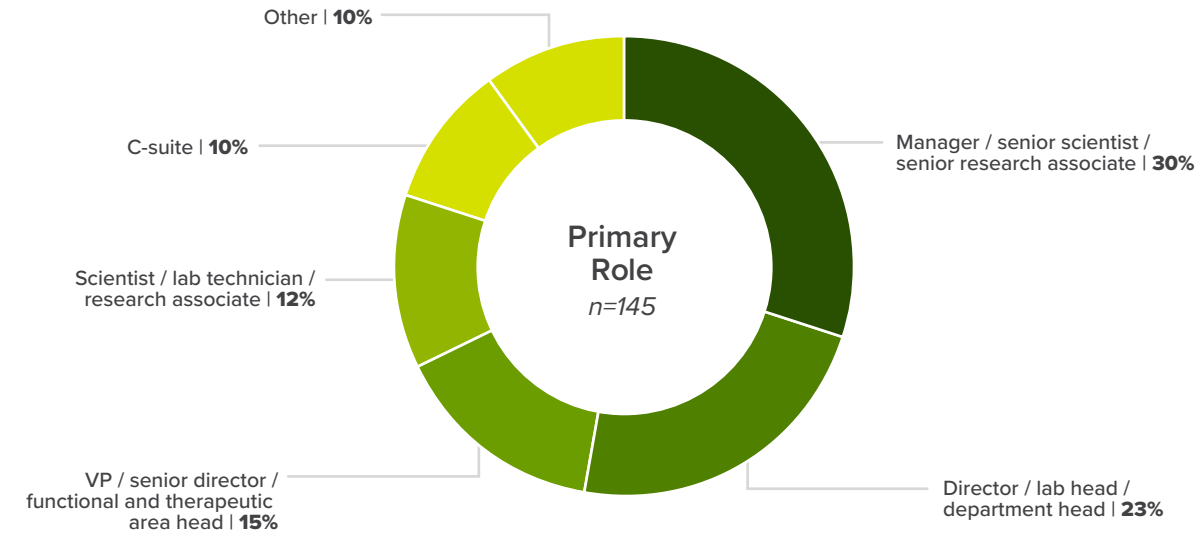
12—25%

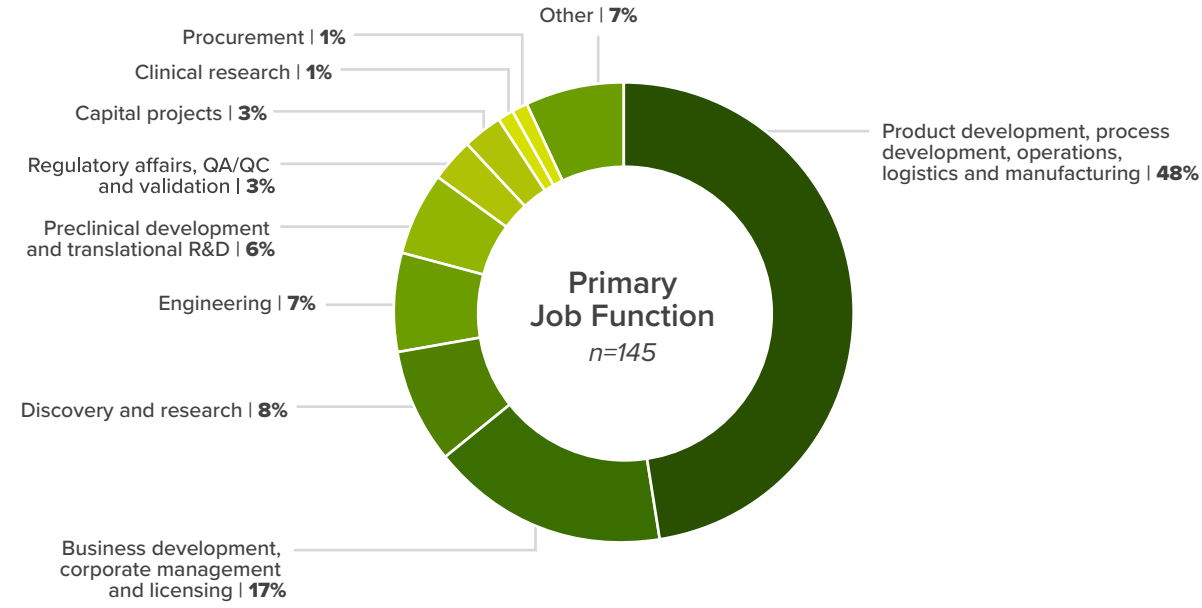
of the floorspace of a heavily siloed facility consists of corridors and airlocks

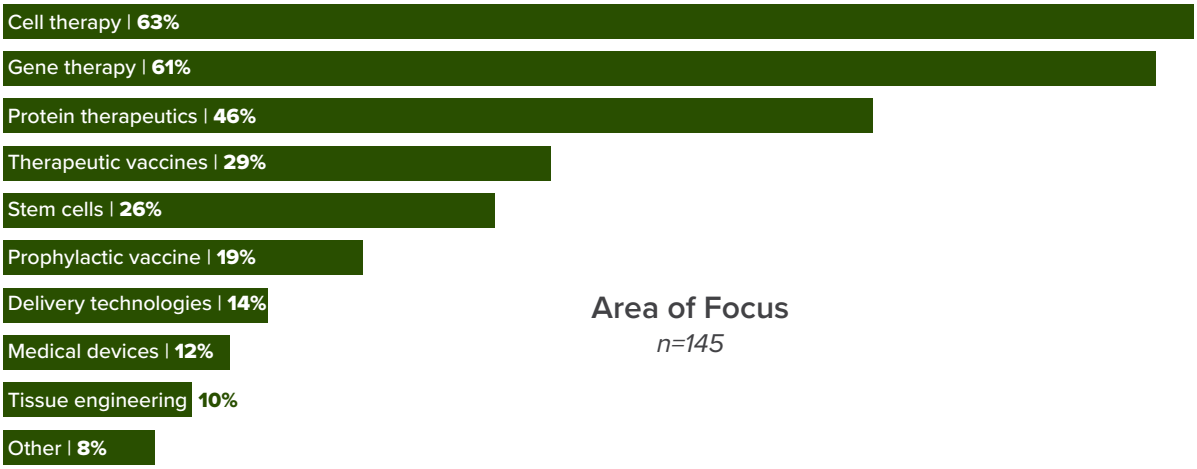
Understanding ATMP regulations, communicating with regulatory agencies and industry peers and embracing closed bioprocessing are key to a successful regulatory strategy. This approach will help with the initial design of the bioprocess that will be used during commercial production and should reduce contamination risk and operating costs, ensure reliable production and smooth the regulatory approval process.

FIRMOGRAPHICS


Investor | 1%
Government | 1%
Other | 1%
Academic / hospital | 10%
Pharmaceutical | 11%
Primary Sector
n=145
Biotech | 54%
Solution or service provider | 23%

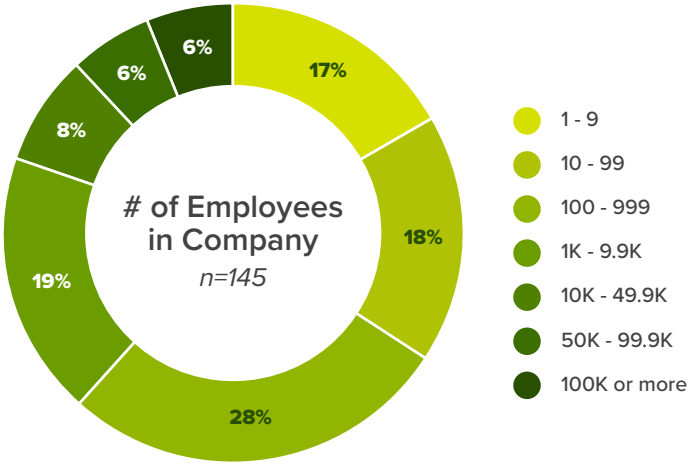

Other | 10%
C-suite | 10%
Manager / senior scientist / senior research associate | 30%
Primary Role
n=145
Scientist / lab technician / research associate | 12%
VP / senior director / functional and therapeutic area head | 15%
Director / lab head / department head | 23%

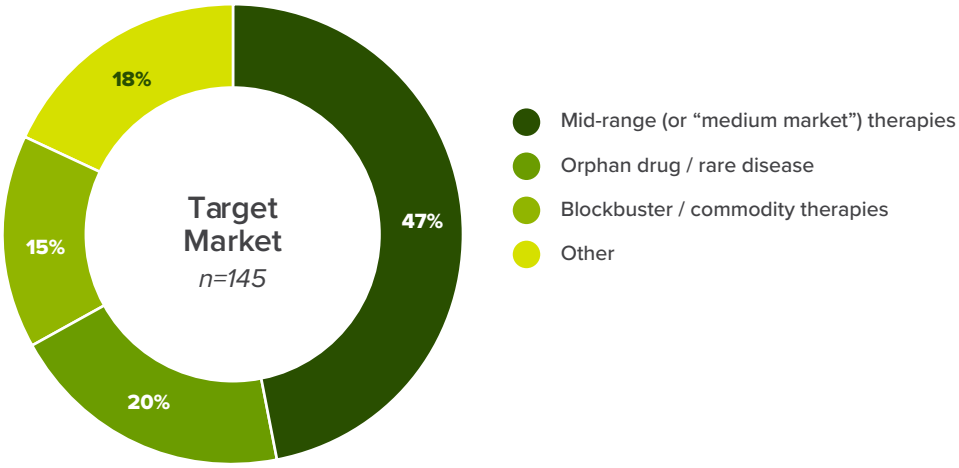

Other | 7%
Procurement | 1%
Clinical research | 1%
Capital projects | 3%
Regulatory affairs, QA/QC and validation | 3%
Preclinical development and translational R&D | 6%
Engineering | 7%
Discovery and research | 8%
Business development, corporate management and licensing | 17%
Primary Job Function
n=145
Product development, process development, operations, logistics and manufacturing | 48%



Area of Focus

n=145





Genetically Modified Cell Therapy Used

n=145

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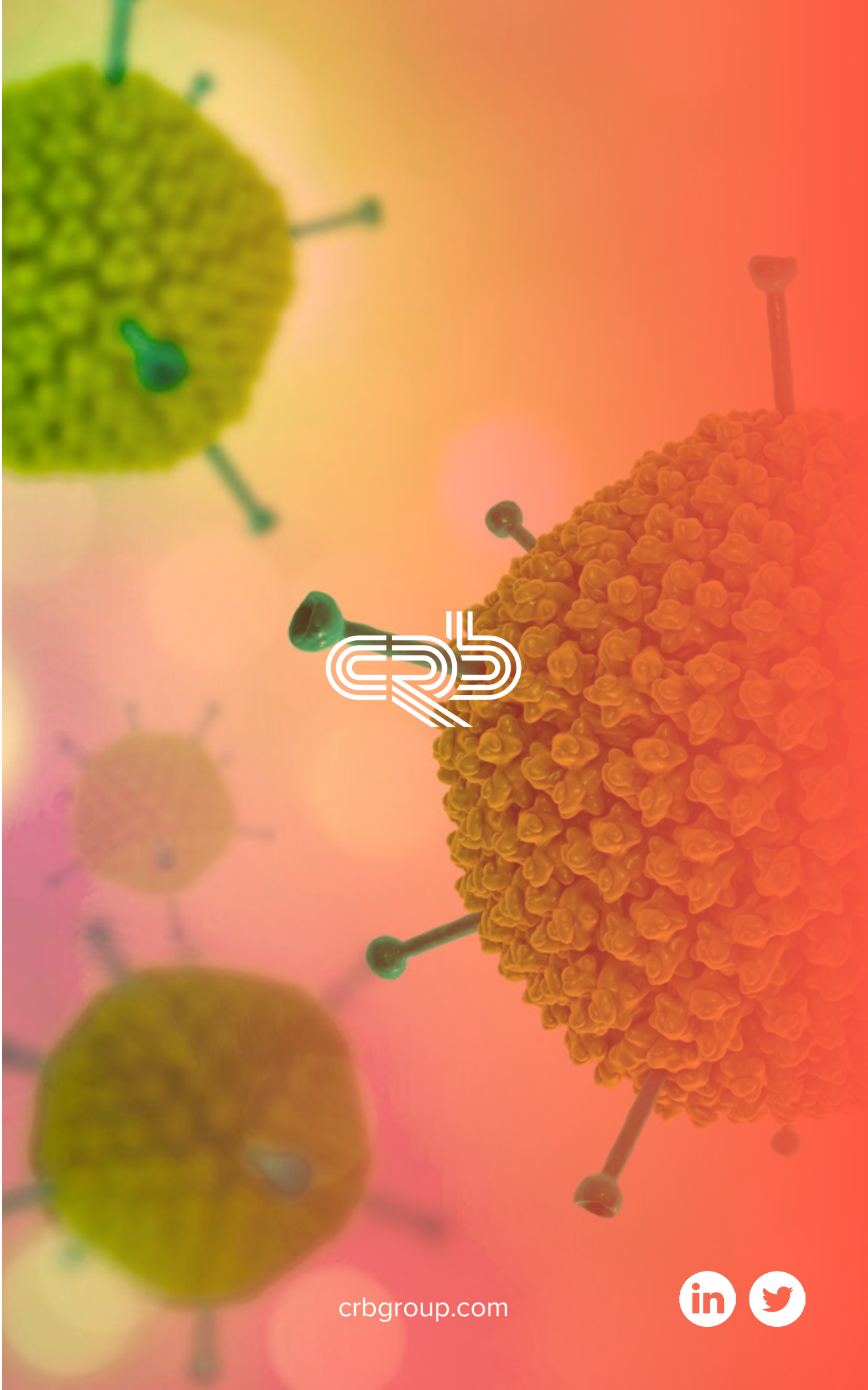

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