2022 Life Sciences

About this Report

Biopharma leaders across the world have long understood speed-to-market as a critical driver for the health of their businesses, and most importantly, the health of patients. From research and development through to commercial-scale manufacturing, a singular focus drives the most successful companies: making timely products, and doing so safely, sustainably, and profitably.

While the COVID-19 pandemic taught us new lessons about the quick and safe delivery of critical vaccines, the learnings from that global shock are only now being understood. They guide our thinking about highly adaptable research and production environments. They inform our collaboration with industry and trade partners in the pursuit of cures. They even teach us to focus inward to make sure our researchers, support teams, and staff have the right tools, technology, and high-level support required to get the job done.

These are among the many factors considered in CRB's newest *Horizons: Life Sciences* report. In the following pages, our subject matter experts analyze the results of an exhaustive survey of nearly 500 industry leaders, who told us about their challenges on many of today's top issues: RNA technologies, cell and gene therapy, therapeutic proteins, automation, data analytics, and more.

This report also represents a major first for our *Horizons* series. This year we expanded our survey to include Europe, where many of our industry's leading organizations are paving the way through innovation, groundbreaking research, and new and dynamic ways of speeding therapies to patients.

CRB is proud to present this survey to you, and we invite your own reflections about how our industry maintains this momentum. We welcome your feedback through our contact page at crbgroup.com, and we wish you a happy and safe 2023 and beyond.

Tim Barba
Chief Operating Officer, Global Technical Operations, CRB

What's next for the life science industry?

In this report: real talk from the front lines of today's research and manufacturing landscape

By: Noel Maestre

My kids discovered *Charlotte's Web* last year. They cheered when we got to the part where Charlotte saves her snouted friend from the breakfast table by weaving magic words into her web: *Some Pig*.

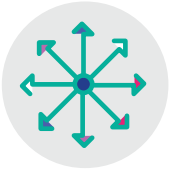
I thought of those words a few months ago, when a surgical team at the University of Maryland transplanted a pig heart into a human for the first time. The animal behind that heart was, indeed, some pig; researchers at the biotech company Revivicor used CRISPR-Cas9 technology to edit 10 of its genes, hoping that their modifications would reduce the risk of organ rejection.

For two months, the transplant recipient lived. Behind those two months lie two decades of research; ahead lies a new era defined by one breakthrough after another, giving hope to patients who had little of it before. Take Yescarta, an engineered T-cell therapy from Kite, a Gilead company, for example—it recently moved from last to second line of defense against non-Hodgkin lymphoma. Meanwhile, Vertex Pharmaceuticals is reporting promising results for the first trial participants who received a potentially curative cell therapy for type 1 diabetes.

Exciting discoveries aren't limited to the cell therapy submarket, though. Last year, regulators approved a first-in-class siRNA therapy from Swiss-based Novartis that could lower cholesterol with just two yearly doses, creating a novel alternative to continuous statin therapy. With these and other amazing new therapies on the horizon, it's a good time to be—and to stay—alive.

Horizons: Life Sciences looks closely at what it takes for companies large and small to keep pace with this rate of discovery. It's the third *Horizons* report in our life sciences series, and the first to invite North American, European, and multinational companies to share their perspectives with us.

Of nearly 500 respondents, a large majority represent research and development roles, upstream of CGMP manufacturing. This gives us a unique look through the laboratory's keyhole; using our survey data, we see that today's life science companies are investing in novel research, pushing against long-established comfort zones, and moving cautiously but steadily toward an advanced standard of care for critically ill patients. In particular, we're seeing a rapidly maturing industry that's in pursuit of:



MORE DIVERSIFICATION:
The majority of our survey respondents have multiple product types in development or in production, from monoclonal antibodies to cell therapies to mRNA vaccines. The days of single-product specialization are receding; as these survey results indicate, today's companies are utilizing the wide array of tools now available to rapidly expand their pipeline and address diverse indications.

MORE MULTIMODAL MANUFACTURING:
In order to build resilience and scalability into their increasingly complex product pipelines, today's life science companies are pushing beyond traditional processing approaches. Whether well-established or just starting up, nearly all of our survey respondents (90%) are developing and manufacturing multiple therapy modalities in a single building, or plan to do so in the future.

MORE PARTNERSHIP:
Pipeline complexity and a push toward multimodal businesses has changed the relationship between owners and contract development and manufacturing organizations (CDMOs). More than half of our survey respondents plan to rely on CDMOs over the next three years, and we're seeing a rise in hybrid models—that is, owners who are offering their in-house manufacturing expertise for hire. Once a provisional resource, CDMOs are now sought after for their expertise and have become a core component of a smart business strategy for life science innovators.

MORE TALENT:
Underscoring each of these high-level shifts in the business of life science manufacturing is an on-the-ground battle for skilled workers. More than half of our survey respondents with cell therapies in their pipeline, for example, say that a lack of trained staff is a chronic weak point. Meanwhile, the nature of in-demand talent is

changing as companies mature towards more automated, AI-driven manufacturing models, with the traditional C-suite expanding to include roles previously unseen in this industry, such as “Chief Data Officer.”

To understand the nuances driving each of these trends and their impact on individual submarkets within the life sciences, we’ve segmented this report into eight chapters. Each one turns a discerning eye to the *Horizons* survey data, giving you a contextualized perspective on what today’s companies are doing to drive success at the lab bench, in the manufacturing facility, and at every point in between.

1 | AN OVERALL PERSPECTIVE ON THE LIFE SCIENCE INDUSTRY

The pandemic incentivized harmonization and attracted more funding to certain segments of the life science industry while introducing greater agility to the regulatory environment. Since then, companies have adopted an optimistic but more cautious approach to ongoing research and discovery. That means carefully weighing the risks and rewards of capital spending and pipeline expansion while continuously pushing for new and exciting discoveries. Join Jake Adams and Peter Walters as they examine this dynamic landscape, using thousands of survey data points to paint a picture of a scalable, flexible future for the life sciences.

2 | RNA TECHNOLOGIES

The rapid arrival of the COVID-19 mRNA vaccines, following years of R&D and clinical success of non-coding oligonucleotide RNAs, catapulted RNA-based therapies into the spotlight. But, in addition to preventing infectious diseases, these technologies—using both non-coding RNA as well as coding RNA—can be harnessed to treat other conditions, like cancer. When compared to other biologics, RNA technologies have the potential to increase speed to market, lower costs, and reduce regulatory requirements. In this article, industry experts David Estapé and Brendan Nichols lead us through the responses from biotech startups and pharma companies that demonstrate burgeoning interest in RNA drug products, expanding investment in RNA production, and the intention to manufacture larger quantities of RNA than ever before.

3 | CELL THERAPIES

More than 300 of our respondents have cell therapies in their pipeline, making this one of the most dynamic—and challenging—submarkets in the *Horizons* survey. Securing a supply of critical materials, managing access to apheresis centers, recruiting trained staff, ensuring reliable results from cell processing equipment—these are the obstacles that are slowing our respondents’ progress from concept to commercialization, but they are also catalysts for new and game-changing strategies. Hear from experts Jan Bondoc and Allan Bream as they examine how researchers are leveraging standardized platforms to maximize the versatility and scalability of their processes, and how decentralized manufacturing will change the future of autologous production—a future that will see cell therapies mature from our last line of defense to an accessible and expected level of patient care.

4 | GENE THERAPIES

Survey respondents at work in this submarket painted a very clear picture for us: change is coming, and it's coming *fast*. Most respondents plan to leap from the small-scale batches necessary for early clinical trials to much larger manufacturing volumes within just three years, and they've got exciting strategies to help them do that. Suspension cell cultures, sterile filtration, stable cell lines, and in-house plasmids manufacturing are attracting an enormous volume of R&D activity among both owners and CMOs as this race toward the commercial market heats up. Experts Devin Hersey and Peter Walters break down this survey data to provide a close and prophetic look at this rapidly maturing field.

5 | THERAPEUTIC PROTEINS

From 100 years of advancements in insulin treatment to the approval of more than 100 monoclonal antibody therapies, the field of therapeutic proteins has come a long way—especially in the last few years wherein trends, technologies, and perceptions in the industry saw significant changes. Whether it's developing strategies for greater process intensification and continuous manufacturing, or the more recent risk-based approaches to process closure, there is much activity and insight coming out of research and development—and our experts, Rob Boulanger and John Rubero, are investigating how developers of therapeutic proteins are strategizing for the future.

6 | DRUG PRODUCT MANUFACTURING

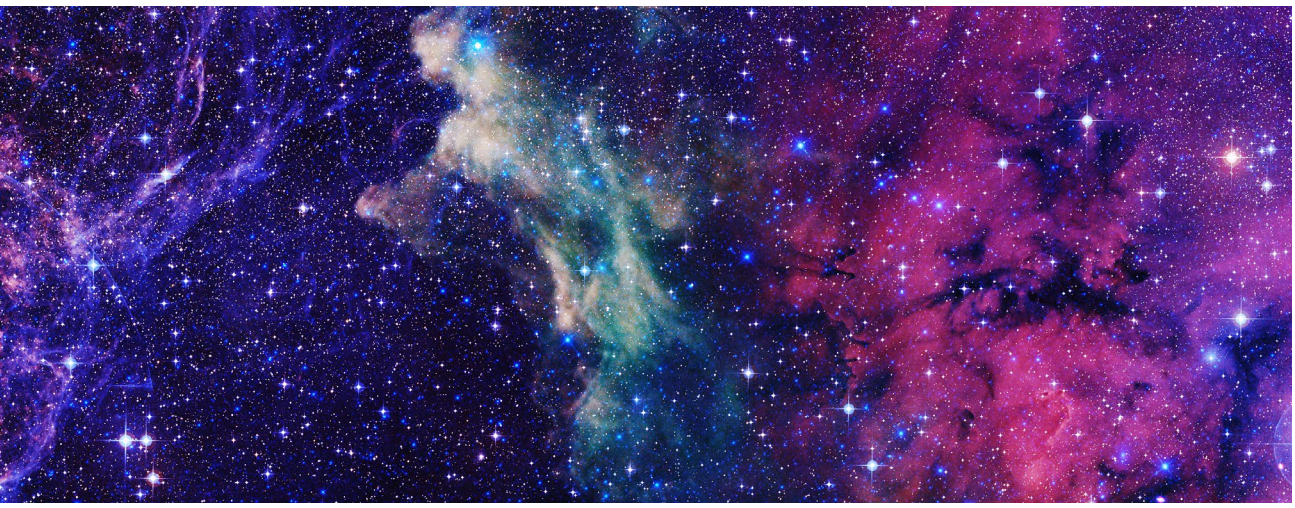
The tailwinds from COVID-19 treatment innovation have ushered in a new era for drug product manufacturing—one that seems to be looking beyond rare disease markets and smaller patient populations to search for the next blockbuster drug; one that is engaging with drug product formulations that are becoming increasingly more complex; and one that is readily embracing automation and online/inline monitoring technologies even at the clinical production operations level. Our expert, Christa Myers, discusses these trends and how they will impact commercial manufacturing in the future, with an eye toward the ultimate goal of getting safe, effective medications to patients as fast as possible.

7 | PHARMA 4.0™

In addition to the innovations that last year's respondents were keen on—tech like artificial intelligence (AI), data analytics, and cloud computing—we are seeing an encouraging evolution in the journey to implementing all aspects of Pharma 4.0, including smart end-user devices, advanced robotics, and digital twins. Companies appear eager to continue the climb to the next level of digital maturity, and a desire to do this quickly. We can see that in the abundance of recent acquisitions that have brought AI innovators into established life science companies. But respondents remain sanguine about how to get there, knowing that budget constraints, organizational reluctance, and a lack of skilled labor might hold them back. Join expert Yvonne Duckworth in a detailed look at today's digitalization landscape and tomorrow's opportunities.

A CASE FOR MODULAR DESIGN

Most of our survey respondents have plans to expand over the next five years, with some indicating an intent to establish a footprint in other countries. Optimizing capital and operations expenditure in these expansion efforts means standardizing operations between sites, expediting regulatory approvals, and remaining agile to demand for new modalities and technologies. Experts Daniel Fritsche and JP Bornholdt explore the benefits of modular design in multi-site expansion, harmonizing the best of customization and standardization.



The next frontier for the life sciences:

The world of *Charlotte's Web*, in which cunning spiders save pigs' lives, may seem like the stuff of fantasy, but the real world can be even stranger—a genetically modified pig with the potential to save a human life, for example.

And yet here we are. Established therapies like monoclonal antibodies continue to find new applications; meanwhile, novel ideas like in vivo gene editing attract record-setting investments and tease a future in which the word "incurable" falls out of use.

With all of this momentum behind it, the life science industry is on the cusp of new and previously unimaginable discoveries, giving us the tools and strategies we need to manage and cure critical illnesses with greater efficacy and repeatability than ever before. This report is a compendium of those tools and strategies, drawn from the perspective of hundreds of life science companies as they race toward a new horizon.

More certainty and fewer moonshots:

How the life science industry is trending for steady, reliable growth

By: Jake Adams and Peter Walters

Section 1

The life science industry is set for a transformative change that will make it unrecognizable in the years ahead—but it won't happen overnight. While the pandemic years delivered thanks to focus, collaboration, and the increased agility of regulatory bodies, its legacy is a framework that supports a slower, more consistent growth.

Today's businesses are no longer thinking "how will we make this process work?" but "will this new therapy be successful?". They're weighing risk and reward more carefully and adding confidence to decisions by testing their options before making bold moves. In short, we're not seeing companies planning to double in size in four to five years. The curve is upward but less steep.

What does this more conservative approach look like in practical terms?

- Producing products at multiple sites;
- renovation of existing spaces;
- leasing cleanroom space;
- companies of all sizes and stripes leveraging CMOs/CDMOs at all stages of delivery; and
- building multimodal operations.

PLANS FOR GROWTH

The overall outlook for the life science industry is optimistic: almost all companies surveyed have plans to expand.

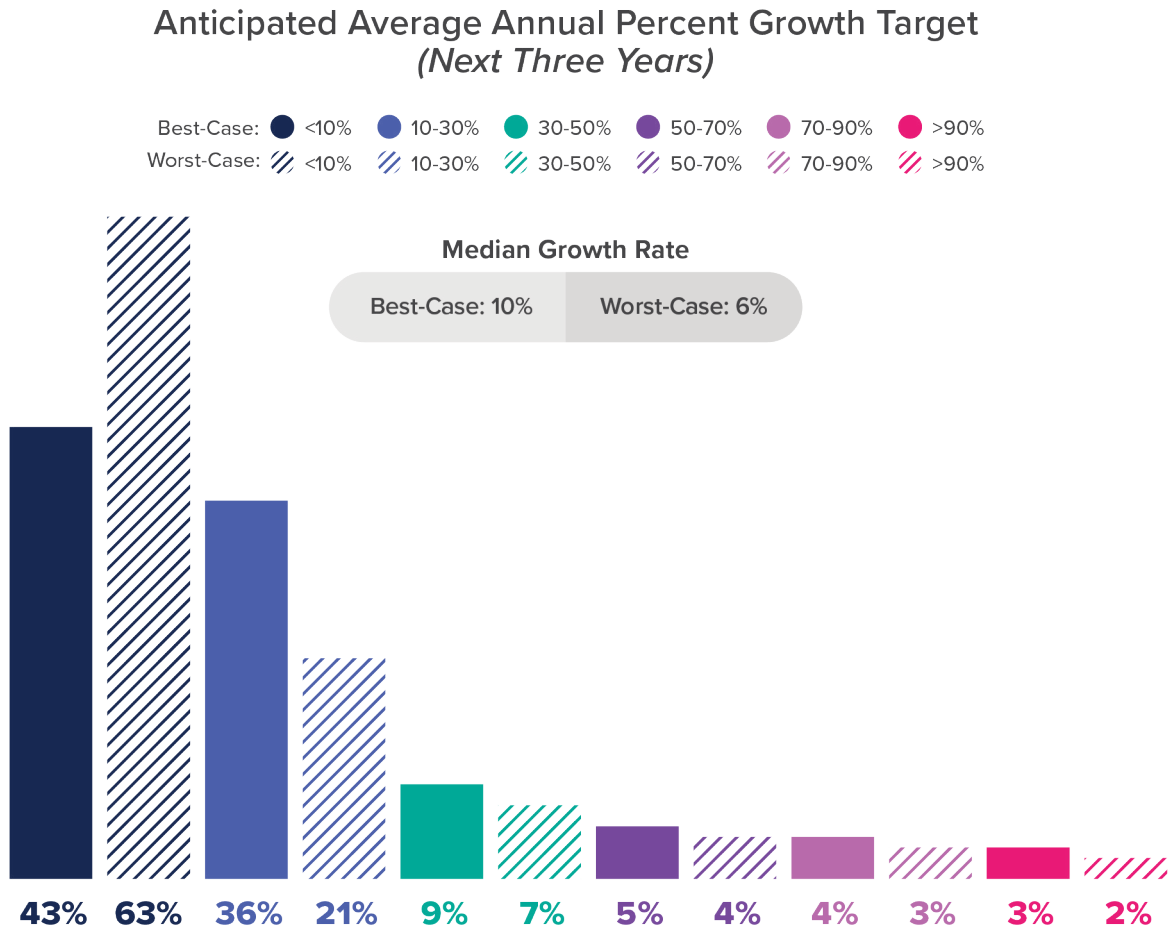
While expansion appears to be a given, growth will be steady and moderate: as a best-case scenario, most companies predict an average annual growth rate of 10% over the next three years. On the flip side, the worst-case numbers sit at 6%.

96%

of respondents have plans to grow CGMP production in the next 5 years

FIGURE 1.1

What is a realistic best-case/worst-case scenario for approximate annual percentage growth over the next three years? (Open entry)



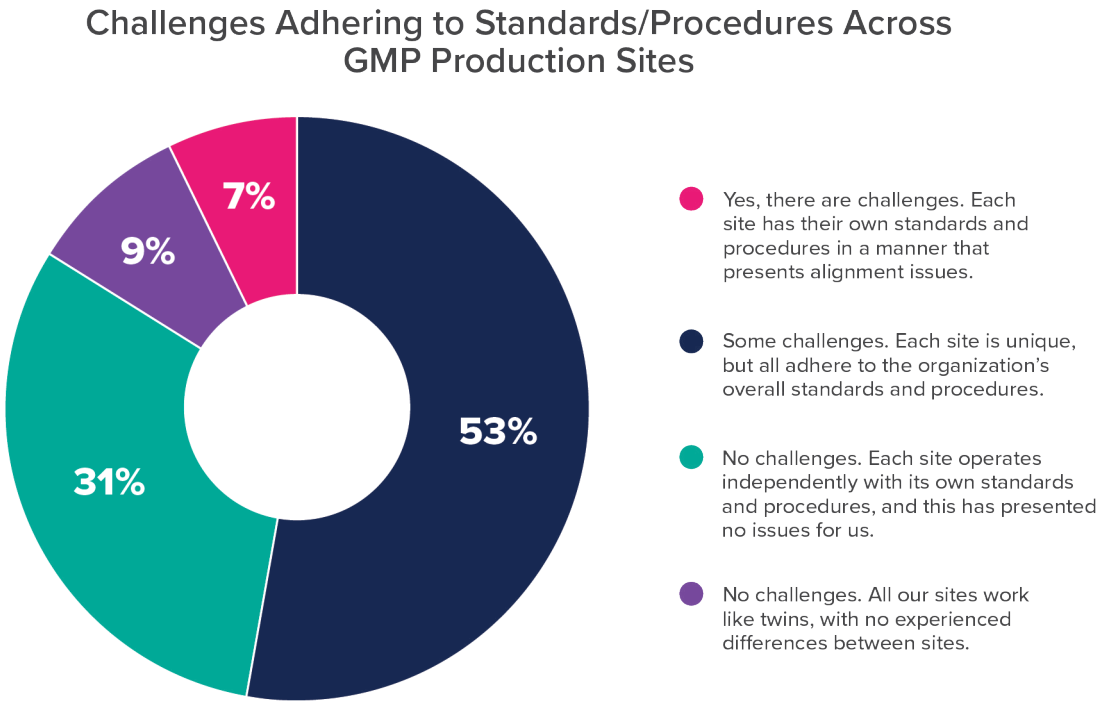
Source: CRB

MULTIPLE SITES

Interestingly, 52% of organizations surveyed house CGMP operations across multiple sites within the same country. As we're all aware, consistency is key for regulators, and this has historically led to challenges with processing across multiple sites. This is no longer the case; however, with 93% of our survey respondents reporting "no" or "only small" challenges to consistency across sites. It's clear this won't be hindering growth prospects: companies can confidently grow out across geographies—and in fact, may even prefer this route for risk mitigation.

FIGURE 1.2

Do you feel your organization experiences challenges in terms of adherence to standards and procedures across your CGMP production sites? (Select one)



Source: CRB

Likewise, our survey reveals that regulatory uncertainty is also not a limiting factor to company growth. A resounding 94% of respondents feel that the regulatory environment is suitable to support growth.

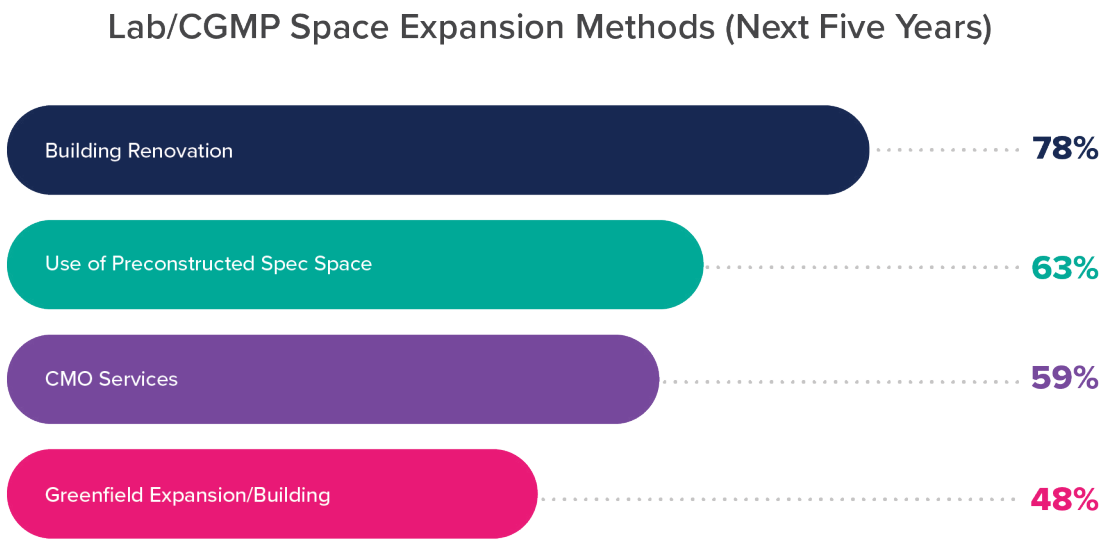
So, the stage is set, with companies reporting plans for growth and confidence in their processes and in regulatory support. The question is, how will these companies increase capacity?

RENOVATING EXISTING SPACES

With lead times and pricing on raw building materials, especially steel, at an all-time high and sustainability increasingly on the C-suite agenda, the advantages of renovating an existing space are clear. This plays out in our data, with renovation being the preferred option for expansion.

FIGURE 1.3

Within the next five years, is your company planning to pursue lab/CGMP space expansion using one of the following methods? (Yes/No)



Source: CRB

These numbers reflect the size of the respondents' company. Not surprisingly, most small and mid-size businesses plan on pursuing lab or CGMP expansion through building renovation, as cost and speed continue to be determining factors. With available capital and a tendency to own swaths of suburban space, large life science companies are more likely to take the longer and more expensive greenfield route to expansion.

LEVERAGING PRECONSTRUCTED SPACE

What is unique is the finding that respondents are significantly more open-minded when it comes to leveraging preconstructed space. This is a potential opportunity in our industry and speaks to an increased flexibility and a risk-averse approach to expansion.

93%

of respondents are using or are open to considering leasing preconstructed space

That being said, while companies may view leasing preconstructed space as a potential low-risk, stop-gap option, it's not necessarily a miracle solution. Finding the space to fit the process, in the right location, at the right time, and for a reasonable price is a tall order. And that's not even speaking to the risk on the side of the developer. For now, while there is significant expressed interest, we don't predict a huge shift in this direction in the immediate future.

CONTRACTING CMO SERVICES

A significant number of respondents—59%—report the use of CMO services as a means of managing production expansion in the next five years. This faster, lower risk, and more flexible approach points again to the emerging tendency to grow with caution, and test processes and therapies before a commitment to expansion.

59%

of respondents report to use CMO services in the next five years

Regardless of company size, the use of a CMO can solve a number of challenges and add incredible value at different phases of development:

- scaling up without the commitment of staffing up and building facilities;
- leveraging specialized platforming approaches and learnings from the CMO's rich experience;
- leaning on a CMO to support on projects outside core competencies; and
- short-term capacity building.

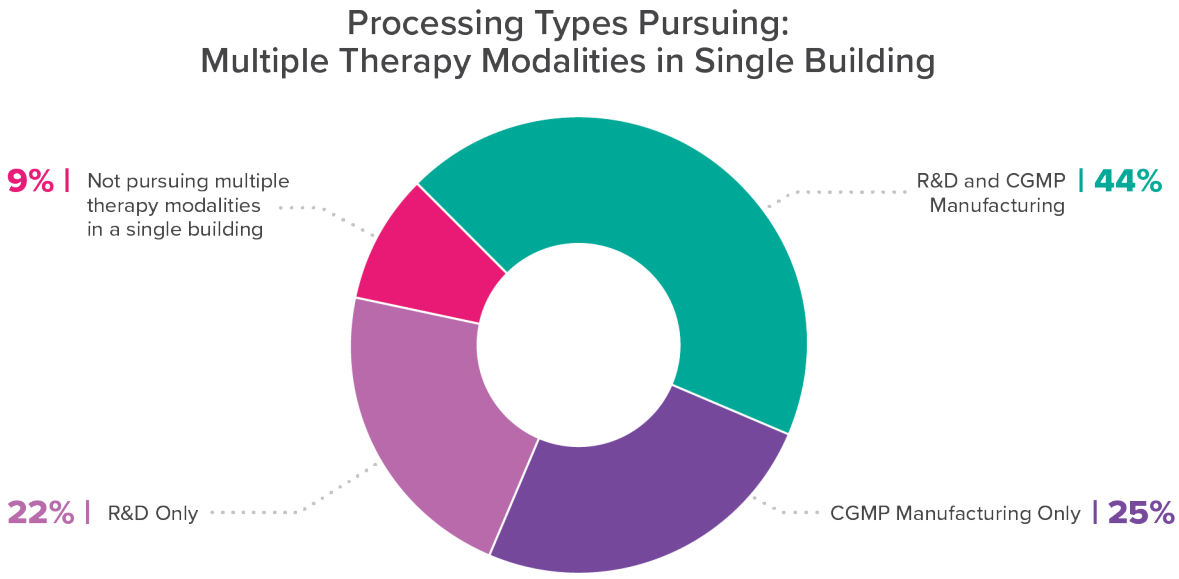
Our results hint at the idea that respondents may be seeking out insight into industry learnings by leveraging a CMO. While a company may have some limited capability to do a specific project in-house, they can benefit from a CMO's experience with other companies by contracting out. Of course, no intelligence is shared between clients, but the CMO may have more efficient processes, market knowledge, and insight that could prove invaluable to a company's expansion.

MULTIMODAL OPERATIONS

What seemed complicated and risky a few years ago now appears to be considered a burden worth the payout. Our survey responses cement the idea that multimodal facilities are trending, even in smaller companies. The expectation may be that it's for R&D purposes, but 69% of the companies surveyed are also looking at CGMP manufacturing that's multimodal.

FIGURE 1.4

What types of processing is your company pursuing with multiple therapy modalities in a single building? (Select one)



Source: CRB

91%

of all the companies are pursuing multimodal within the same building

Again, this approach mitigates risk: the saying about eggs and baskets comes to mind. But what also might be happening here is that companies are more comfortable with the idea of obtaining regulatory approval for a multimodal facility. While there are still limited in-market examples of these facilities, those that are operating are successful, opening the possibility to more. The business model makes sense, and now there are regulatory precedents in place.

Note that this may also be a driver for renovation being a leading form of expansion: transitioning single modality facilities to multimodal operations.

Confident and clever

The theme ‘proceed with caution’ permeated through all of our survey findings. While companies are expanding across the board, they are taking measures to mitigate risk and make a solid business case before investing significant time and money into new products.

We expect that the use of CMOs alongside in-house R&D and CGMP production will continue, and in fact be a rule rather than an exception in the years to come. There may not be huge spikes in growth or a feverish rush to ‘get in early’, but the industry we see is confident, constantly progressing, and delivering great outcomes.

Expressing enthusiasm for RNA:

Today's life science companies are taking RNA-based therapies well beyond vaccines

By: David Estapé and Brendan Nichols

Section 2

Over the last two years, RNA-based therapies have become a household name due to the COVID-19 mRNA vaccines, which followed on the successes of non-coding RNA therapies such as oligonucleotides and siRNA. These technologies have immense potential to fight a wide range of conditions, including infectious diseases and cancer. In the case of short non-coding RNA, they are finding a place as treatments for a wide variety of diseases with underlying genetic causes, many of which are untreatable by other modalities. When compared to other biologics, some RNA technologies have the potential to increase speed to market, lower cost of goods, and reduce regulatory requirements.

In addition to these benefits, the data we collected from industry experts shows that there is great interest in RNA drug products, more current and impending capital investment in RNA manufacturing, and a plan to produce greater masses of RNA than ever before. In short, RNA-based therapies hold great promise for today's innovators—and the patients who count on them.

Key Takeaways:

- The interest in RNA products continues to grow for a variety of therapies
- Companies are pursuing a range of synthesis approaches and delivery systems
- Significant current or planned investment in new manufacturing capacity at different scales in the short term
- A substantial proportion of new manufacturing capacity is intended for large-scale production (>10 kg/year)

RNA DEFINITIONS

Coding RNA

These long mRNAs are synthesized using in vitro transcription.

Non-coding RNA

These short RNA molecules are traditionally chemically synthesized using solid phase synthesis. Here are a few common examples among the many non-coding RNA applications:

- Oligonucleotide conjugates: adding a targeting ligand to an oligo to improve pharmacokinetics
- Small interfering RNA (siRNA): double-stranded RNA that inhibits gene expression via degradation of mRNA in the cell
- Aptamers: single-stranded oligos that bind to target proteins and altering function
- Single guide RNA (sgRNA): used in CRISPR-Cas9 gene editing systems
- Antisense RNA: short RNA complementary to mRNA that blocks translation

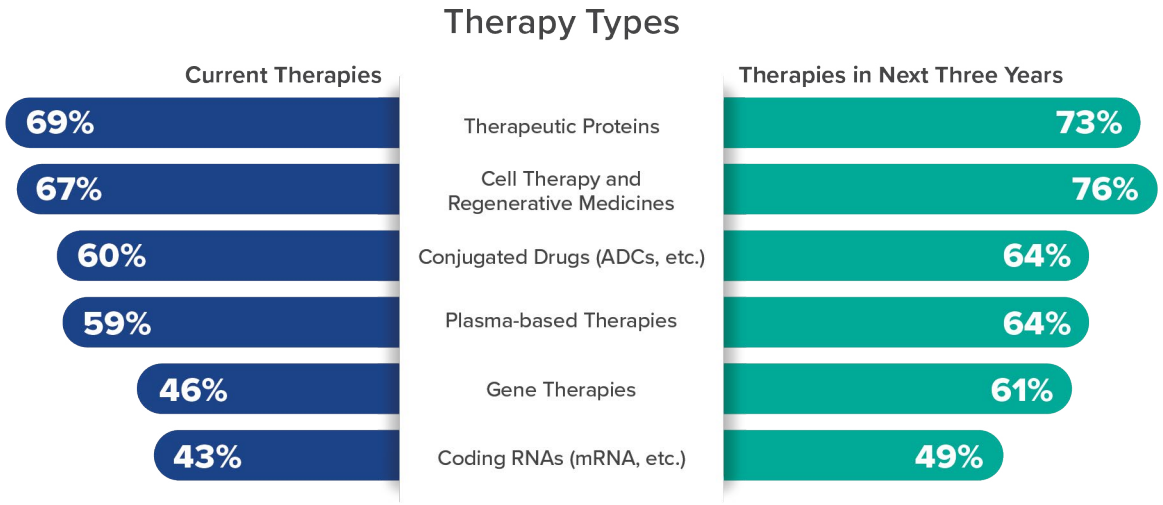
RNA PRODUCTS ARE IN THE QUEUE AND GAINING TRACTION

While RNA therapies are relatively new to approval and commercialization compared to more established therapeutic modalities, more than half of the survey respondents (55%) said their company was currently developing and/or manufacturing a RNA-based therapy. They also indicated interest is increasing and should continue for at least the next three years (Figure 2.1). We've watched these percentages grow steadily over the past two years, which is no surprise given the success of the Pfizer/BioNTech and Moderna mRNA vaccines, as well as the commercial approval of several new oligonucleotide therapies.

FIGURE 2.1

Left: What product types are your company's site currently developing and/or manufacturing? (Yes/No)

Right: What therapy types does your company's site anticipate developing in your product pipeline within the next three years? (Yes/No)



Source: CRB

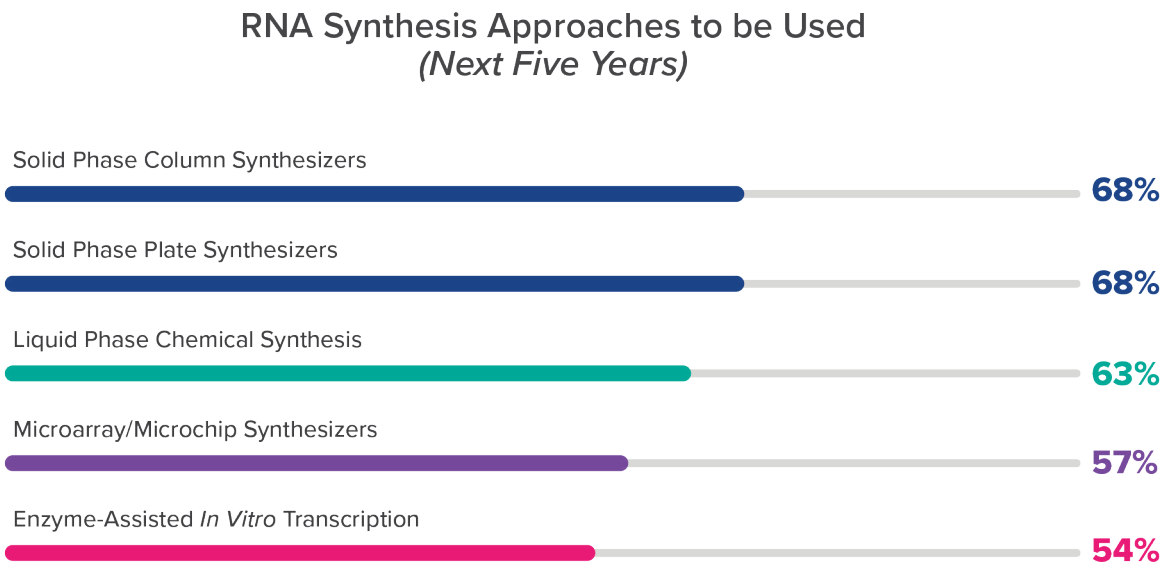
MULTIPLE RNA SYNTHESIS APPROACHES WILL BE USED

The length of the target RNA molecule influences the synthesis approach chosen. Two-thirds of the respondents plan to use solid phase synthesis to make RNA in the next five years, the technology that is the backbone of oligonucleotide and short non-coding RNA production (Figure 2.2). Respondents from CMOs were even more likely to choose solid phase synthesis, in keeping with the enthusiasm we've seen among them for this technology.

Liquid phase chemical synthesis is an umbrella term for a few different approaches, including enzyme-assisted in vitro transcription (IVT). Given that IVT is the manufacturing process used to synthesize the large masses of mRNAs used in COVID-19 vaccines, it is surprising that it had the fewest responses (54%). In contrast, the response shown for liquid phase chemical synthesis (63%) was much higher than we expected. This response may reflect the large proportion of processes being actively developed in R&D, where we're seeing a significant amount of investment in liquid phase chemical synthesis. This is in keeping with the strong drive towards classical biochemically inspired routes of RNA manufacturing that are less solvent intensive than solid phase synthesis.

FIGURE 2.2

Is your company planning on using the following RNA synthesis approaches in the next five years? (Yes/No)



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PRIMARY DRIVERS FOR CHOOSING A SYNTHESIS APPROACH

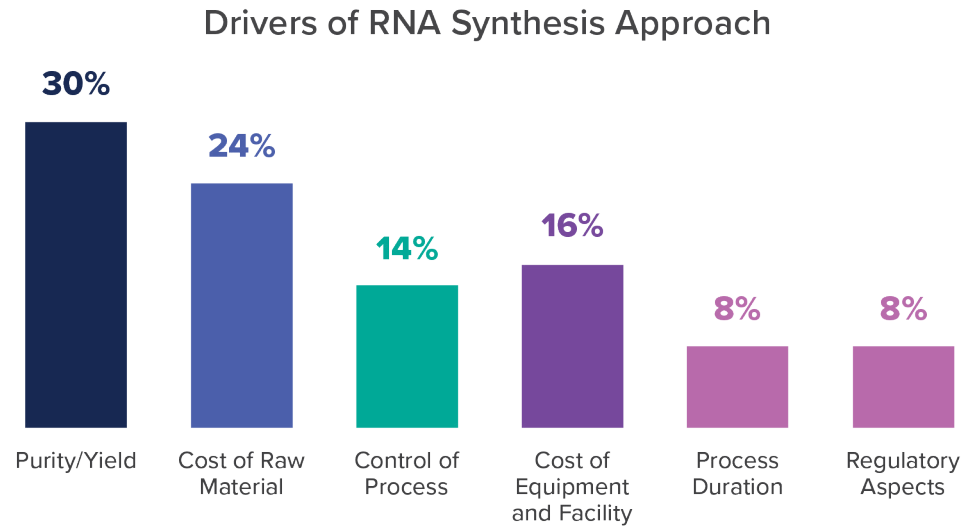
Respondents ranked purity and yield as the most important drivers (30%) when choosing a synthesis approach (Figure 2.3). Those at CMOs were more likely to choose this as the most important (34%) compared to project owners (20%).

Regulatory thresholds of RNA purity and yield are still being developed and can differ substantially between mRNA and short non-coding RNAs. This is a result of the variation in, and complexity of, impurity profiles among differing methods of RNA synthesis. The final manufacturing process for any RNA has not been standardized yet and it could be that different companies will continue to tweak synthetic processes and try new technologies. With so much rapid change in the industry, it's quite possible that a novel liquid phase synthesis process could supplant solid phase synthesis as the preferred mode of manufacture for short non-coding RNA. In this regard, regulatory aspects are a concern for more project owners (15%) than CMOs (5%).

Cost of raw materials is the major consideration for project owners (28% compared to 20% for CMOs). This is driven by expensive polymerase and capping enzymes, nucleosides, chromatography resins, and lipids for mRNA (e.g., COVID-19 vaccines) and by nucleosides, solid support, and chromatography resins for short non-coding RNA.

FIGURE 2.3

What are the primary drivers of your company's chosen RNA synthesis approach? (Rank order)



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COMPANIES ARE PURSUING A RANGE OF RNA DELIVERY SYSTEMS

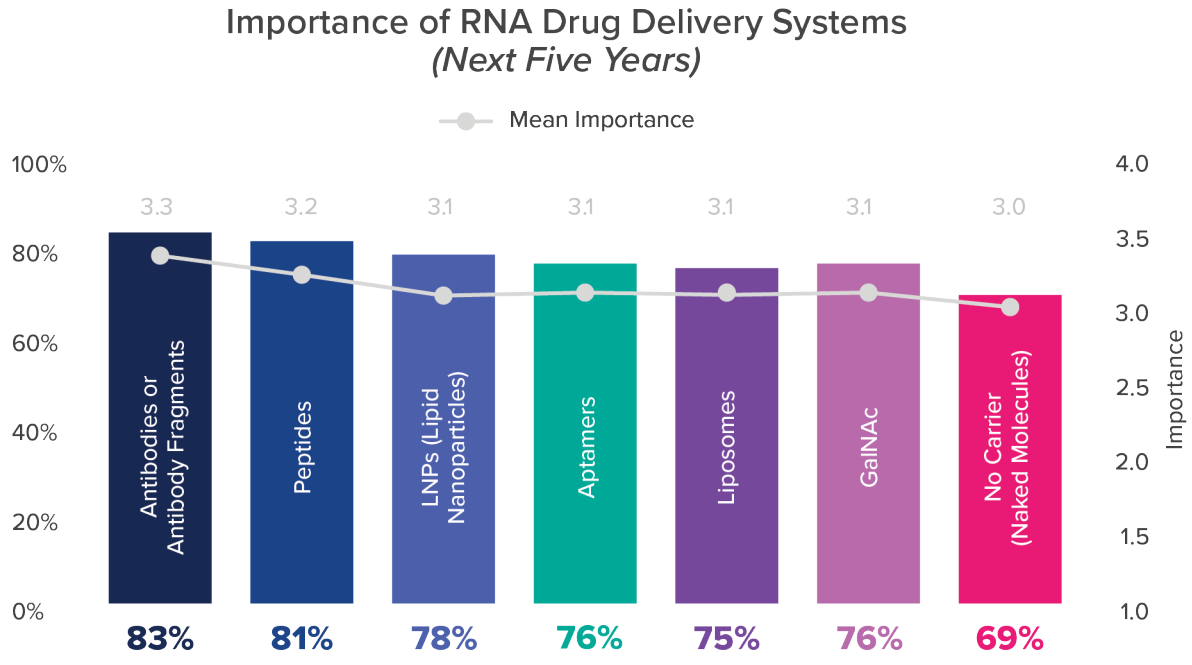
The wide range of RNA drug delivery systems noted as important by our respondents suggests attention is being paid to all delivery techniques and confirms what we've been seeing in the industry (Figure 2.4). While GalNAc conjugation has been the leading approach for targeted delivery of non-coding RNA due to its unique ability to concentrate in the liver, antibody, peptide, and aptamer conjugates are the subject of a huge research effort across the industry to target other cell types.

Therapies using mRNA and long non-coding RNA are delivered via lipid nanoparticles (LNPs) or liposomes, while short non-coding RNAs use all the delivery systems listed (although LNPs and liposomes are least relevant).

Even "no carrier" had a large response, reflecting the significant interest we've seen in the industry. Oligonucleotides and single-stranded antisense oligonucleotides don't necessarily need to be delivered to a specific cell type as long as they're injected with sufficient concentrations into the body. Several companies are planning to use a no carrier approach, using either a targeted injection or intravenous injection.

FIGURE 2.4

How important are each of the following RNA drug delivery systems for your company in the next five years? (Multiple choice)



Source: CRB

RNA FOR GENE EDITING AND GENE THERAPY? LET'S GO!

RNA is a versatile molecule, able to be harnessed for a variety of different therapeutic platforms. Of course, given the success of mRNA vaccines to combat COVID-19, we'll likely see more of these for preventative vaccines to combat flu and other recurring infections. This is reflected in the three-quarters of respondents using or considering using RNA for preventative vaccines (Figure 2.5). This is a logical consequence after the success of COVID-19 vaccines as the industry looks to expand the application of mRNA vaccines to other diseases. The safety and effectiveness of this type of mRNA drug have been shown.

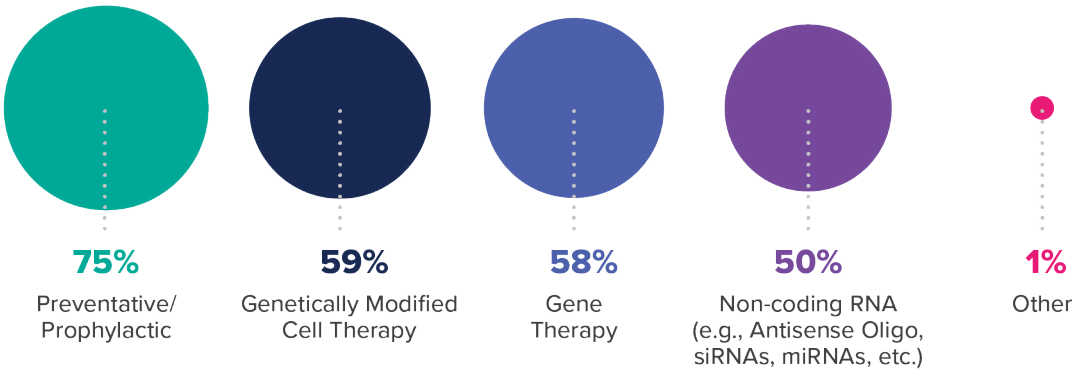
Some may have wondered where the RNA market will go once COVID-19 passes and people no longer need boosters. But what this data tells us is that there is interest in all platforms and that life science companies are taking a multimodal approach to their pipeline planning.

Take gene editing technologies, which 59% of respondents indicated either using or planning to pursue within five years. This is a huge jump in interest in the industry from a couple of years ago. Genetically modifying cells using RNA is of great interest in R&D right now, and there have been successful Phase II Clinical trials for gene editing technology, leading many others to enter this field. We find the interest expressed here in using RNA for gene editing extremely exciting as this offers tremendous promise as potentially curative therapies for genetic diseases.

FIGURE 2.5

Which of the following therapy types is your company using or considering leveraging RNA-based technologies for within the next five years? (Yes/No)

Therapy Types to Use/Consider Leveraging RNA-Based Technologies *(Next 5 Years)*



Source: CRB

Similar interest was seen for gene therapy (58%), which aims to replace a missing or defective protein in cells. While this has most often used DNA transfection, it can also be accomplished by giving mRNA to patients, in whom it is transiently expressed. Companies are developing mRNA protein replacement therapies for a range of conditions, including cystic fibrosis, heart disease, and cancer. One example of in vivo gene therapy in clinical trials uses the CRISPR gene editing system to treat ATTR amyloidosis. It includes mRNA encoding the Cas9 protein and a single guide RNA that targets a defective TTR gene. This points to the growing focus on in vivo gene editing, which has seen substantial financial investment recently.

INTENDED PRODUCTION SCALE HAS GREATLY INCREASED

The scale of RNA production that companies are planning to implement in the next five years has skyrocketed since last year (Figure 2.6). They are also targeting a range of production scales, reflecting the amounts needed for different types of therapies and patient populations. In fact, many life science companies are diversifying their portfolios by including many RNA modalities. This includes everything from microgram quantities for personalized medicine, what is needed for clinical trials, and up to large-scale commercial production (>10 kg per year).

Notably, last year, none of the respondents in our *Horizons: Life Sciences* report said they were aiming to produce more than 10 kg of RNA per year. Those numbers have exploded, with a majority now saying their company is planning to produce more than 10 kg per year and 35% expecting their company to produce more than 100 kg per year.

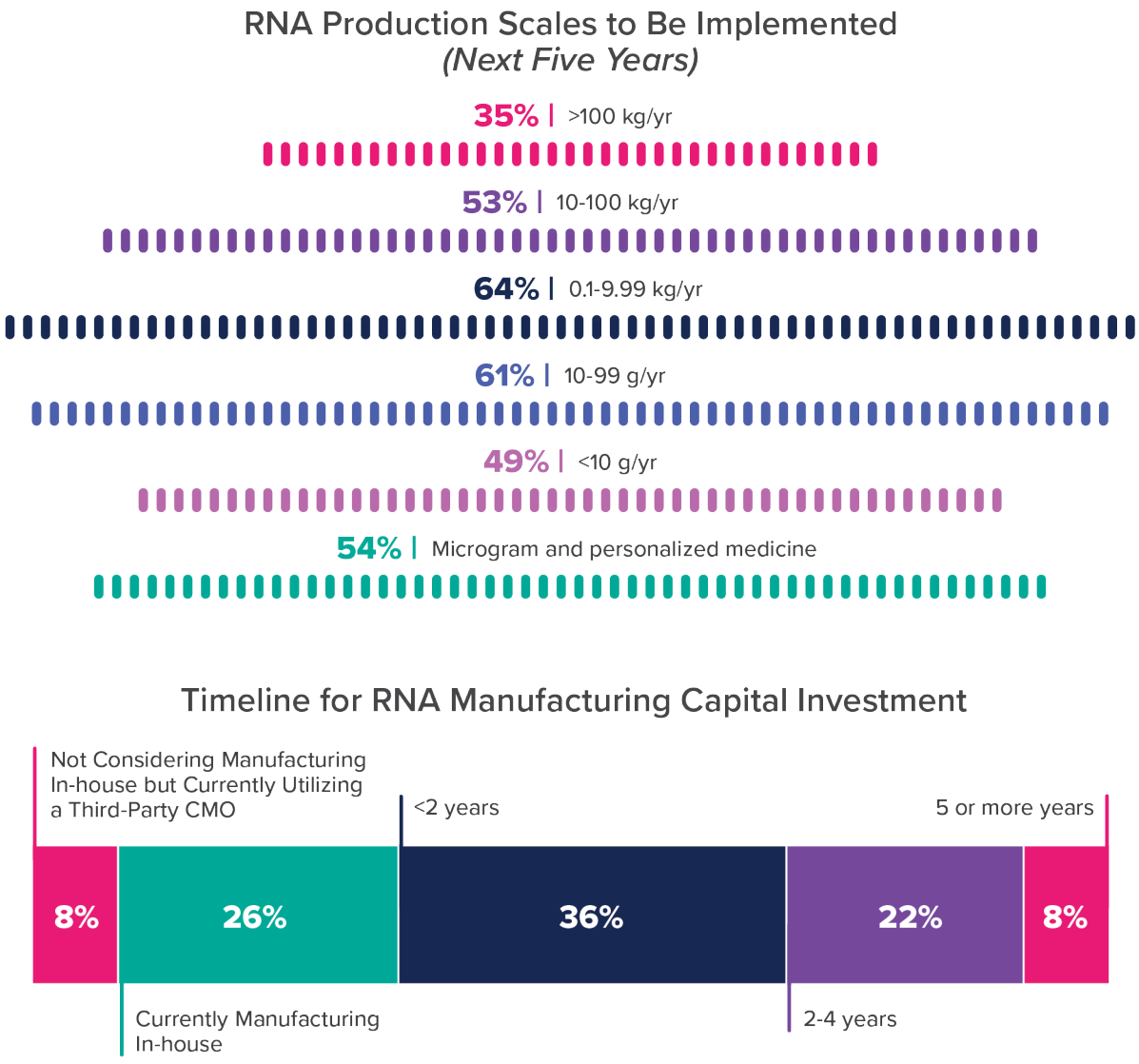
Given the intention of a large number of companies to produce >100 kg of RNA per year within the next five years, we wonder whether there will be adequate manufacturing space to meet demand. While production capacity for mRNA has ramped up to meet domestic vaccine needs, there may not be enough capacity when the supply needed to meet global demand is considered. This really will depend on how the pandemic continues to play out and the ways governments develop pandemic-readiness plans. For non-coding RNAs, in the last year or so we've seen a substantial financial commitment from CMOs to bolster large volume (>100 kg/yr) manufacturing capacity around the globe, and a likewise sizable investment from technology originators.

We expect investments made over the next two to four years will result in robust global manufacturing capacity. This is reflected in the low percentage (8%) of respondents selecting a timeline for capital investment of at least five years (Figure 2.6). However, there are approximately 80 oligo therapies currently in Phase II or III Clinical trials, targeting both large and small patient populations. It may just take a single resounding clinical success from this group to reset global manufacturing needs.

FIGURE 2.6

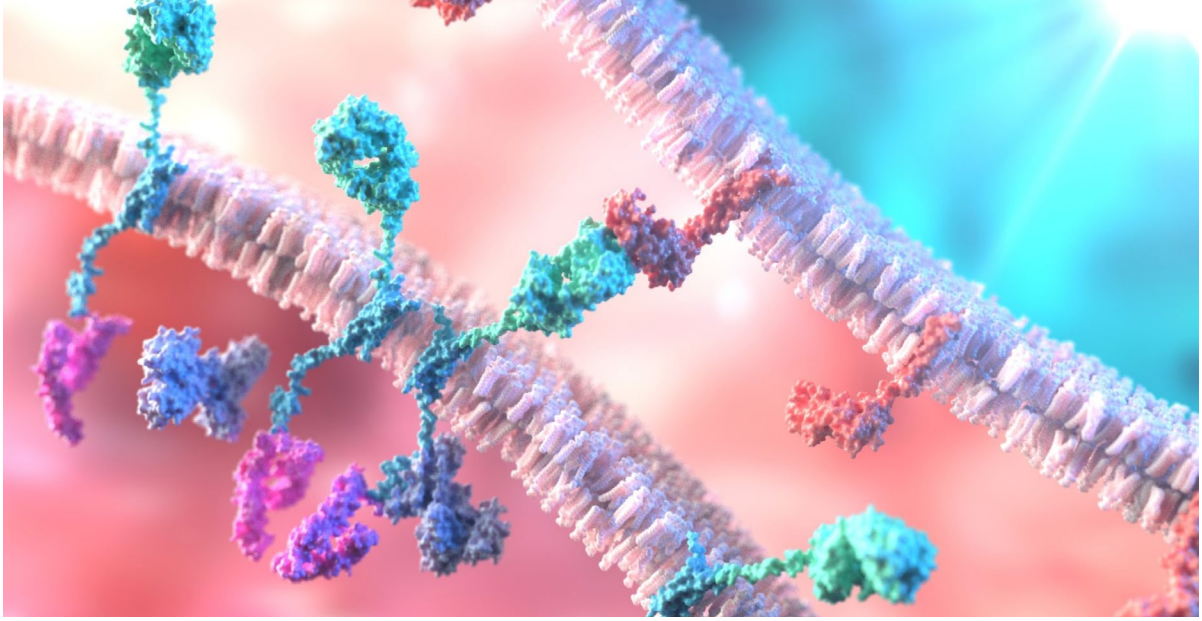
Top: Is your company planning to implement the following RNA production scales in the next five years? (Yes/No)

Bottom: If your company is considering at least some in-house RNA manufacturing, what is the timeline for capital investment? (Select one)



Source: CRB

Almost two-thirds (62%) of those who are currently developing and/or manufacturing RNA said their companies are either already manufacturing in-house or intending to invest capital to do so within the next two years.



Harnessing RNA for future therapies

RNA-based therapies have evolved from an interesting idea to real-world applications that are saving lives. Back in 1990, when Dr. Katalin Karikó first proposed using mRNA in gene therapy, few believed her ideas could ever be used therapeutically. It took her and scores of other scientists three decades of dedicated research to arrive at the success of the COVID-19 vaccines.

We are eager to watch as life science companies continue to harness these discoveries to treat a wide array of diseases with RNA products. Startups, mid-range, and large pharma companies alike are embracing RNA therapies. They are looking to produce more RNA, using a range of synthetic approaches and delivery systems. And, from what we've seen from our surveyed experts, enthusiasm for these revolutionary technologies will only continue to grow.

From benchtop to bedside:

How cell therapy innovators are preparing for commercial success

By: Jan Bondoc and Allan Bream

Section 3

When 6-year-old Emily Whitehead became the world's first pediatric patient to receive CAR T-cell therapy, her care team explained the complex treatment in memorable terms: they were sending cells from her own body to a cancer-fighting boot camp.

Since that breakthrough moment, researchers on the frontier of cell therapy manufacturing have been going through their own kind of boot camp. A turbulent supply chain, a capacity crunch, a talent shortage—defeating these obstacles and closing the distance between promising trial results and real-world patient outcomes requires immense skill and a far-seeing strategy.

That strategy may look different depending on the cell therapy type in play. For example, both autologous cell therapies, which are patient-specific, and allogeneic cell therapies, which develop from healthy donor cells and provide off-the-shelf therapeutic potential, are candidates for a standardized manufacturing platform; in fact, almost all of the 300+ respondents who answered the cell therapy segment of our survey plan to embrace process standardization in the near future. But autologous cell therapy manufacturers have an extra ace up their sleeve: decentralized production.

The idea is to address the challenges that arise when making small, personalized cell therapy batches—limited scalability, complex cold chain logistics, time pressure—by moving the manufacturing process as close to the bedside as possible. A full 96% of

our survey respondents are considering this strategy, and more than half expect to implement it within the next five years.

Standardization, decentralization—in a manufacturing landscape as complex as a life-or-death game of 4D chess, this is the future. With good advanced planning, certain manufacturers can leverage one or both strategies to lower their cost of goods and improve patient access. Check and mate.

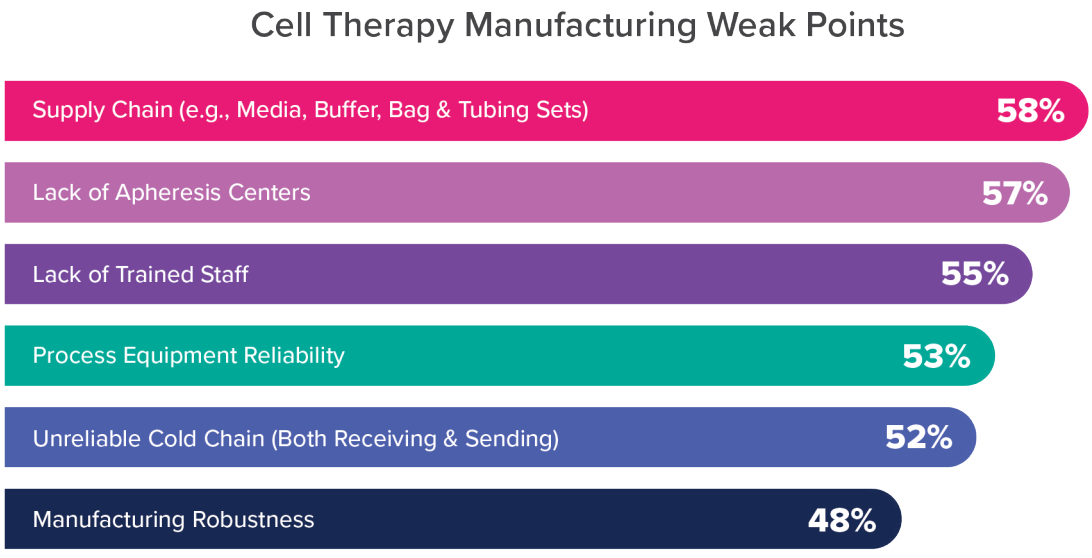
SIGNIFICANT CHALLENGES ON THE ROAD TO SUCCESS

Before it can save a patient, a cell therapy must first survive its own lifecycle. The process of developing, testing, transporting, and administering these therapies is extraordinarily complex, and each step introduces new risks: competition for talent could drive costs higher; unreliable cell processing equipment could cause a serious quality issue; a bottlenecked supply chain could fatally impede forward momentum.

The main challenge is that there is no main challenge. When we showed survey respondents six potential weak points in their manufacturing approach, they identified each one as more or less equally concerning (Figure 3.1). With so many hurdles to clear, each as tall as the next, it becomes difficult to identify priority areas where investments of time and money are likely to pay off—and without priorities, risk creeps in.

FIGURE 3.1

Do you see any of the following as a weak point in successful cell therapy manufacturing? (Yes/No)



Source: CRB

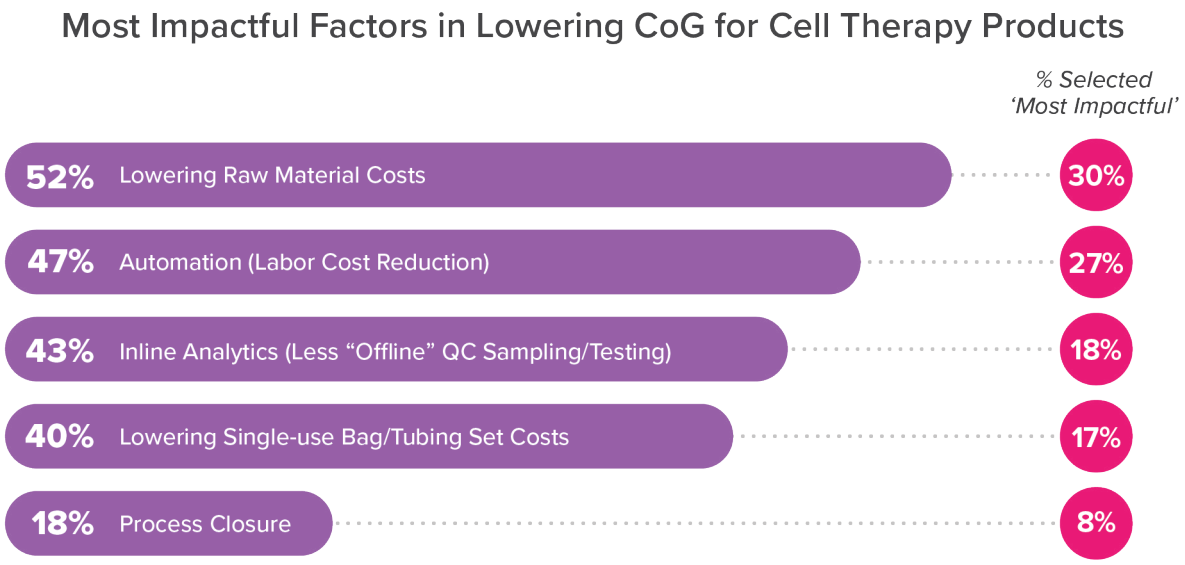
There is no silver bullet here. Throwing money at these challenges won't solve them—or, at least, it will create new problems by inflating the cost to patients.

Take supply chain turbulence and its impact on acquiring critical raw materials and single-use components as one example. Survey respondents ranked this as their top barrier; at the same time, 40% identified it as an impactful factor in lowering their cost of goods (Figure 3.2). Meanwhile, another supply-related headache ranks in the number two spot of top barriers: a lack of apheresis centers.

Supply chain headaches on one side of the equation, patient access on the other—a difficult problem to overcome. Manufacturers can work toward a solution by identifying their future needs with support from an integrated Enterprise Resource Planning (ERP) system, and by strengthening their supplier network to ensure those needs are met. A scalable labor strategy, on-site warehousing, capacity planning in partnership with apheresis centers and other third parties—these complementary strategies are also mission-critical.

FIGURE 3.2

Which two factors will have the largest impact on lowering cost of goods for cell therapy products? (Select two)



Source: CRB

Fortunately, there are just as many opportunities coded into Figures 3.1 and 3.2 as there are challenges. While a lack of trained staff ranks high as a weak point in Figure 3.1, for example, automation ranks nearly as high as a driver for cost control in Figure 3.2. These are symbiotic concepts: the more manufacturers are able to

automate their manufacturing approach, the smaller their staffing burden. By leaning into solutions that both address a chronic weak point and lower their cost of goods, manufacturers can begin clearing the road for a sustainable scaling approach—even while navigating the early stages of research.

THE CHALLENGE OF SCALABILITY:

Don't overlook the advantages of process closure

There's one notable surprise in those Figure 3.2 results: very few respondents ranked process closure as an impactful strategy for lowering their cost of goods.

This may be a function of the job type. Most survey respondents work in R&D roles rather than commercial production; in a fast-moving, operator-driven research lab where teams are focused on the fine line between immediate success and failure, the benefits of process closure may seem distant and immaterial. But it's only by looking across that distance that a cell therapy innovator can transform ideas at the research bench into effective and accessible treatments at the bedside.

The good news: 90% of those who responded to our *Horizons* survey are conducting their research within large or medium companies, where examples of mature, sophisticated commercial approaches are likely abundant. By harnessing that sophistication, cell therapy innovators can avoid locking themselves into growth-limiting processes, technologies, or supply dynamics.

Process closure, a key enabler of cell therapy manufacturing, is an important component of this sophisticated approach to scalability. It all comes down to bringing a commercial state of mind into the research lab and aligning early process and equipment decisions with big-picture manufacturing objectives.

Key Takeaway:

Don't overlook the long-term value of process closure while focused on short-term goals in the research lab. It's a key enabler of streamlined, automated commercial cell therapy production, and it's much easier to implement if it's embraced early on.

THE CHALLENGE OF PARTNERSHIP:

Owner-CDMO relationships are strong, but headaches remain

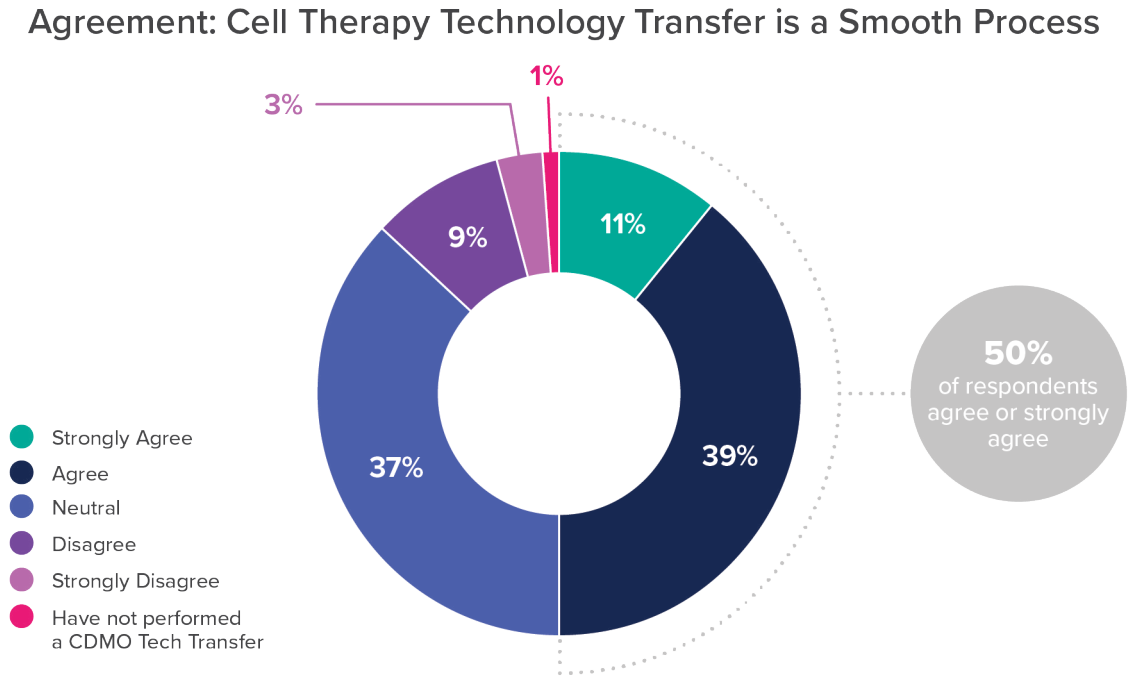
While they push for scalability and more efficient manufacturing approaches, many manufacturers from across modalities are turning to CDMOs as strategic partners—52% in fact, according to our survey results.

Fortunately, half of the cell therapy manufacturers in our survey agree that the technology transfer process between CDMOs and project owners is smooth (Figure 3.3). We would have expected a much lower satisfaction score if we'd asked this question just a few years ago, but the landscape is changing; the "D" in CDMO—a relatively recent addition—signifies, in part, a shift towards a more customer-centric

partnering approach in which cell therapy innovators and third-party manufacturers co-develop processes in a climate that's more collaborative and less adversarial.

FIGURE 3.3

To what extent do you agree or disagree that cell therapy technology transfers from CDMOs to in-house manufacturing is typically a smooth process without many issues? (Select one)



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There's an interesting nuance running underneath this big-picture view, though. When we segmented our data by owner, CDMO, and hybrid (a CDMO with their own in-house products), we began to see that in cases where friction does exist, it's usually the owner who perceives it (Figure 3.4), and it's most often related to a lack of transparency or unexpected changes (Figure 3.5). CDMOs should take note: consistent, transparent communication could be an important differentiator when competing for contracts.

FIGURE 3.4

To what extent do you agree or disagree that cell therapy technology transfers from CDMOs to in-house manufacturing is typically a smooth process without many issues? (Select one)

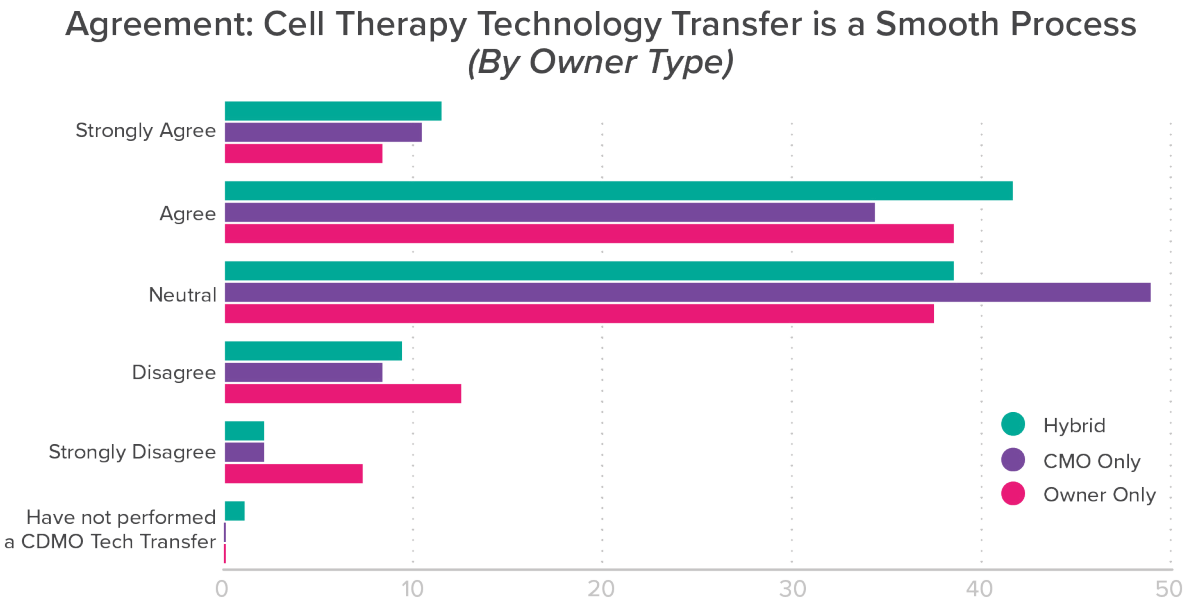

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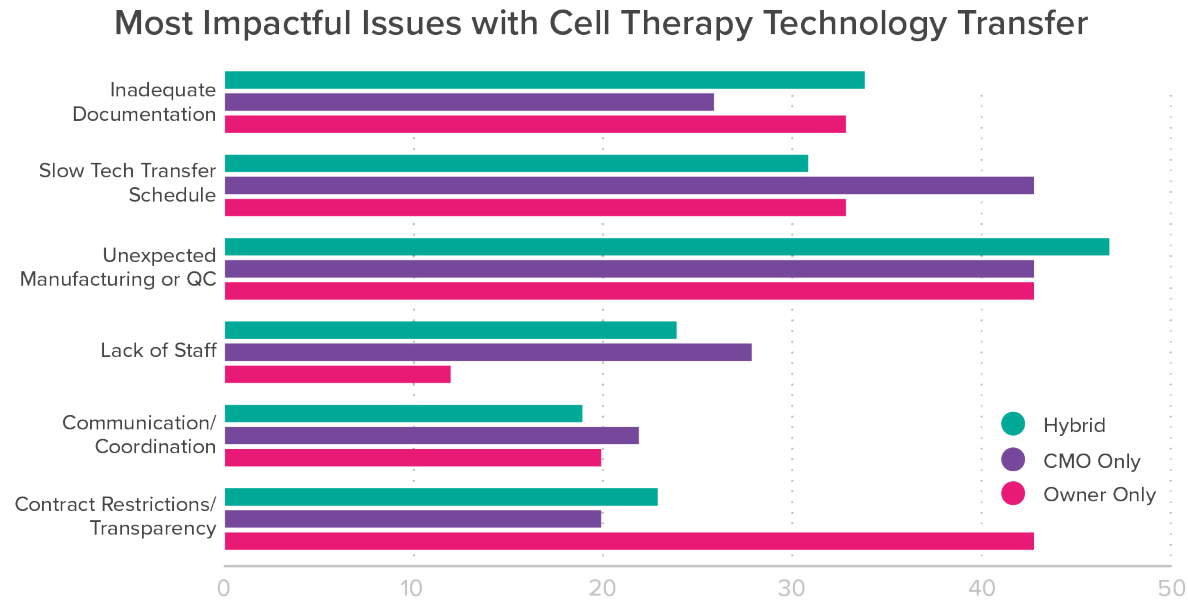
FIGURE 3.5

What have been two of the most impactful issues your company has had with cell therapy technology transfers from a CDMO to in-house manufacturing (Select two)?



Source: CRB

Good communication alone won't pave the way for success, however. To ensure forward progress, whether working with partners or not, cell therapy manufacturers need to align their research and development activities with long-term strategies that are scalable, and patient focused.

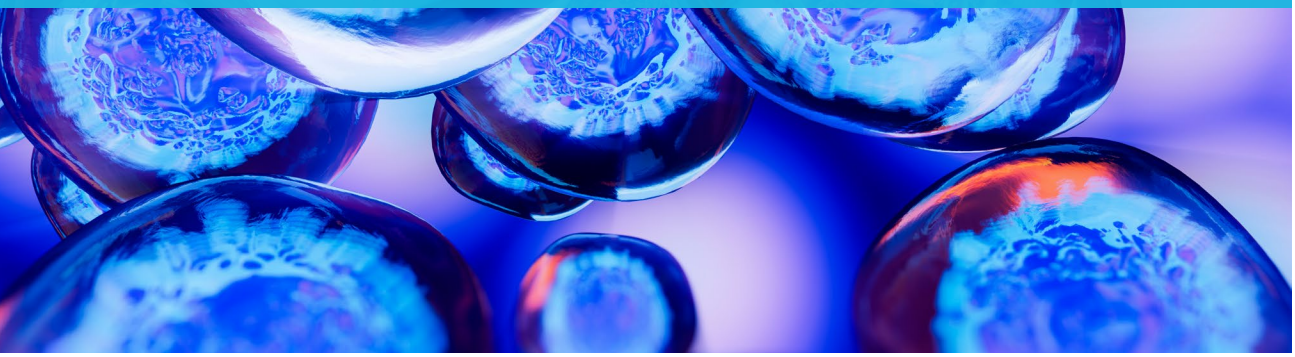
That means planning for a standard, platformed manufacturing approach. For autologous cell therapy manufacturers, it may also mean aligning that standardized approach with a future in which therapies are made not in a remote facility but right inside the clinical environment.

Key Takeaway:

Where there's friction between CDMOs and owners, it's the owner who's most likely to feel it—and it usually comes down to a breakdown in communication. This is an opportunity for CDMOs to differentiate themselves by prioritizing a clear, transparent partnering approach.

THE SOLUTION:

Standardized cell therapy manufacturing for all, and a decentralized approach for autologous

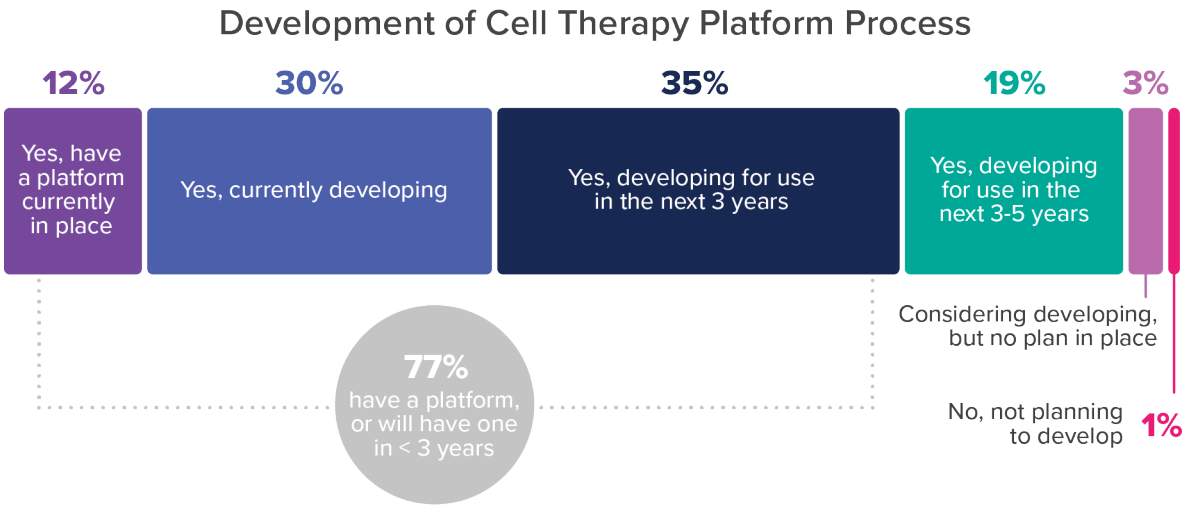


STANDARDIZATION: SYNERGY FROM STEP ONE

In our work with clients, we've detected a surge of interest in platformed cell therapy manufacturing. Our survey respondents have made this observation concrete: 77% have a cell therapy platform process in place, or they plan to develop one within the next five years (Figure 3.6). Of course, larger companies have a head start in that direction, but even most smaller companies—who might be inclined to prioritize short-term speed over long-term process innovation—plan to have a standardized platform in place in the next three to five years (Figure 3.7).

FIGURE 3.6

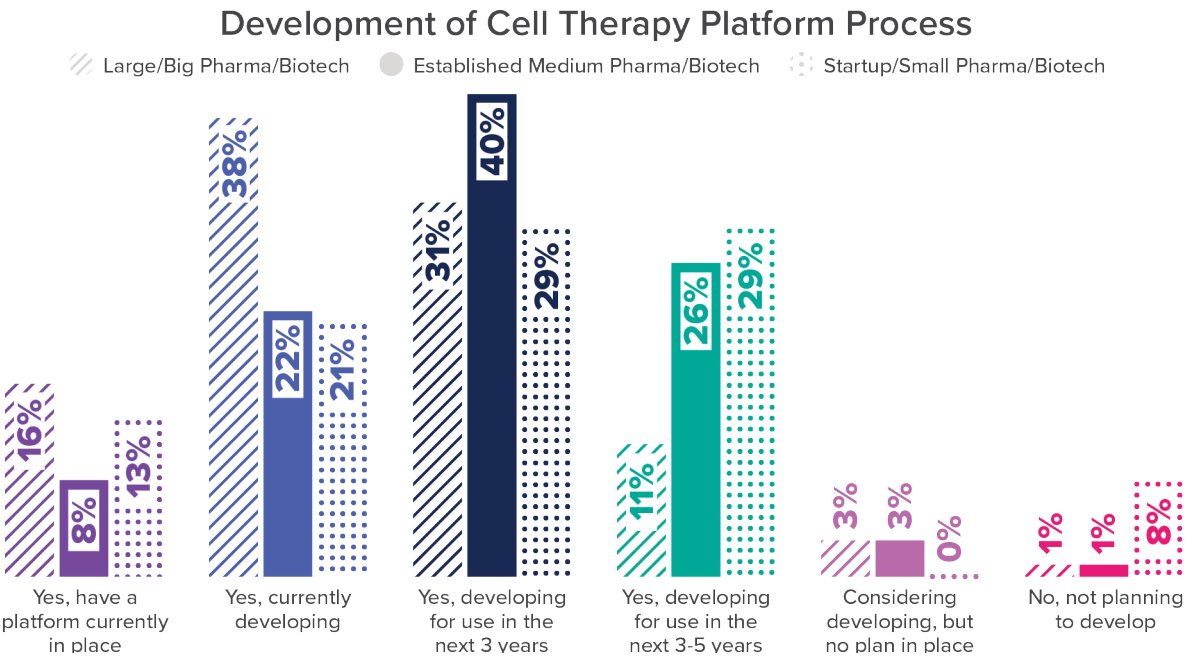
Is your company developing a cell therapy platform process (i.e., the same manufacturing process that can accommodate different transgene and target different indications)? (Select one)



Source: CRB

FIGURE 3.7

Is your company developing a cell therapy platform process (i.e., the same manufacturing process that can accommodate different transgene and target different indications)? (Select one)



Source: CRB

In a competitive landscape that puts pressure on innovators to move fast while pursuing multiple indications using an adaptive platform, this shift makes sense. By investing in a standardized process, cell therapy developers can juggle multiple product profiles while streamlining the commissioning, validation, and regulatory approval pathway. This is a win-win scenario: for patients, it means receiving therapies much more quickly; for manufacturers, it means a greater chance of sustaining long-term commercial success.

That commercial success starts in the research lab, where developers can leverage process standardization to address many of the factors outlined in Figure 3.2. For example, instead of relying on a third-party supply of raw materials such as viral vectors, companies should position themselves for rapid future growth by planning for in-house vector manufacturing. As they move through clinical testing and toward commercial-volume production, this early investment could pay for itself several times over.

In addition to saving money, a platformed process also has the potential to save time. By engineering a standardized process that's adaptable for different products, companies can accelerate staff training, for example, which may ease some of the labor headaches identified in Figure 3.1 while improving quality and reliability overall. Partnering can also become easier with standardization; the potential for unexpected changes—a source of frustration, as reported in Figure 3.5—diminishes when both CDMOs and owners are unified around the same standard, versatile manufacturing process.

Of all the advantages driving today's push for standardization, the most promising may be the role it could play for autologous cell therapy manufacturers as they move out of the capital-intensive facility and into the clinical environment.

DECENTRALIZATION: AUTOLOGOUS CELL THERAPY MANUFACTURING AT THE BEDSIDE

Unless cell therapies are accessible to patients, they won't benefit anyone. Even so, we were surprised by the momentum behind point-of-care manufacturing models; 94% of cell therapy manufacturers who responded to our survey are at least considering hospital or clinic partnerships, and more than half are either actively engaged in one already or are pursuing it within the coming five years (Figure 3.8).

94%

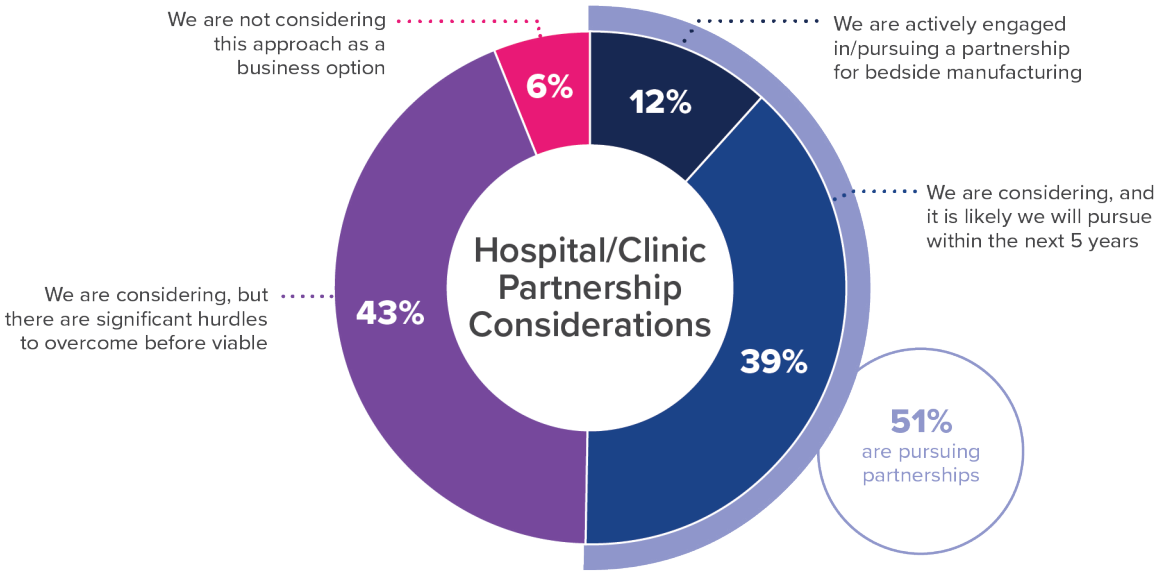
of cell therapy manufacturer respondents are at least considering hospital or clinic partnerships

For autologous cell therapy manufacturers, the advantage of decentralized bedside manufacturing is its simplicity. In contrast, a more centralized manufacturing approach requires companies to move critical materials between a patient's bedside, an apheresis center, a manufacturing facility, and often a third-party lab for release testing—a journey that requires extensive cold chain logistics and a complex chain of

custody that can withstand multiple handoffs. Any vulnerability in this delicate ballet—including a problem as trivial as rush-hour traffic—could disrupt the manufacturing schedule and affect the therapy's efficacy, which in turn could directly impact critically ill patients for whom every hour counts.

FIGURE 3.8

Is your company considering partnering with a hospital or clinic to provide bedside cell therapy manufacturing within the next five years? (Select one)



Source: CRB

By shrinking the distance between that patient and the autologous cell therapy manufacturing process through a decentralized approach, companies can remove many of those intermediate steps, which in turn eliminates significant risks and improves patient access.

Key Takeaway:

Decentralized manufacturing is the future of autologous cell therapy, and its success depends largely on efficient, standardized manufacturing processes and the emergence of advanced technology to support those processes.

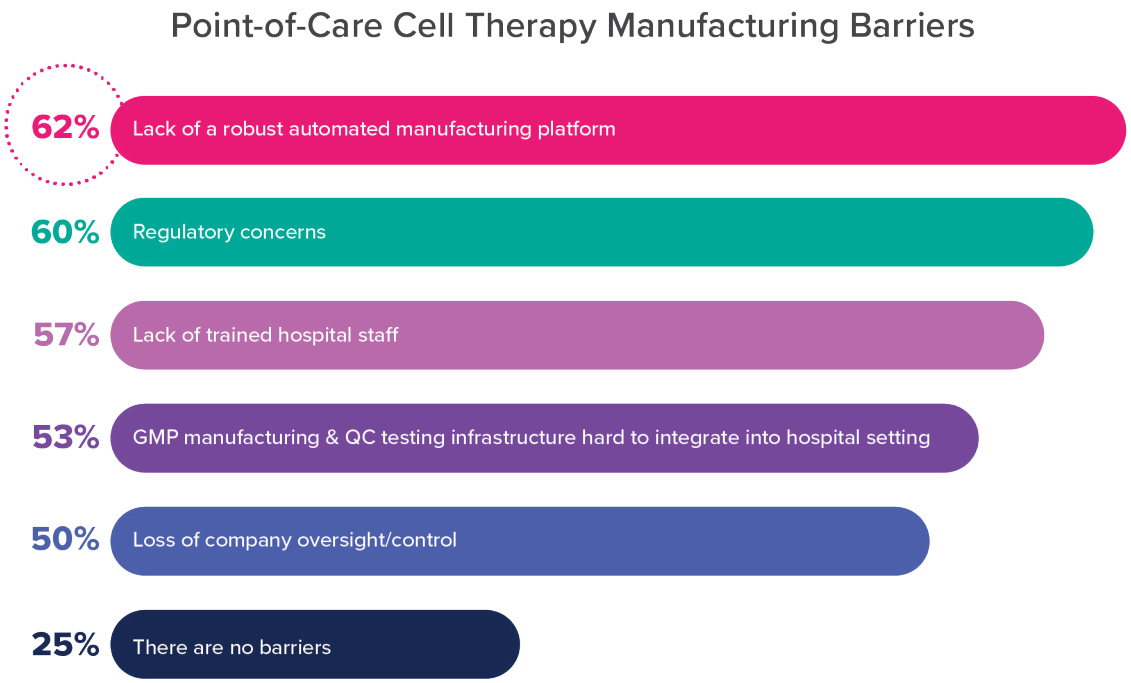
Reaching that point, though, is about more than developing a standardized process and putting it inside a hospital. For one thing, cell therapies—like all drug products—require extensive product release testing. Manufacturers typically perform the bulk

of this process, while some specialty tests can be outsourced. With careful upfront capacity planning, it may be possible to leverage a hospital's own quality clinic to meet this need.

In addition to a strategy for managing support functions like release testing, companies pursuing decentralized manufacturing are also waiting for durable cell process equipment that can support a standardized approach within the small spaces available in hospitals and clinics. As we can see from the top result in Figure 3.9, that wait continues.

FIGURE 3.9

Do you believe each of the following factors are barriers to point-of-care cell therapy manufacturing at hospitals/clinics (Yes/No)?



Source: CRB

Fortunately, cell process equipment suppliers are actively innovating in this arena. Some new process-in-a-box solutions are already on the market, and others are imminent; as these solutions become more mainstream over the next few years, autologous cell therapy innovators will have more opportunities to move their operation to the bedside—or close to it.

The benefits of this shift towards decentralized autologous cell therapy manufacturing are significant:

- **A leaner labor model:** A platform that leverages end-to-end automation and process closure will simplify and streamline the bedside model, making it an important enabler of decentralized manufacturing. This platformed approach also plays a role in lowering the staffing burden and accelerating operator training, which will help manufacturers overcome the talent crunch facing all life science companies today.
- **Ongoing quality control:** Although outsourced release testing will remain an important final step in the manufacturing process, overall quality control will become easier with support from robust inline analytics and other automated features built into the self-contained platform.
- **Lower cost of goods:** Without having to build and maintain enormous highly regulated cleanroom environments, autologous cell therapy producers can do much more within a much smaller footprint. A decentralized model could also free them from the burden of transporting their product between the patient and the manufacturing site, which reduces their resources, costs, and risks. Each of these advantages will positively impact the cost of goods.

Of course, the greatest beneficiary of this shift is the patient. In a future that includes standardized and decentralized manufacturing, the right cell therapy may be identified, manufactured, and delivered in a much shorter timeframe—which could mean a much longer life.

The future of cell therapy manufacturing is already here

The boot camp that prepared young Emily Whitehead's cells to fight her pediatric cancer was a success. She's now celebrating 10 years cancer-free, and as the number of cell therapies in late-stage development grows, more critically ill patients across diverse indications have reason to hope for good news of their own.

Meanwhile, cell therapy innovators have been learning valuable lessons from the "boot camp" of rapid growth and commercialization. They're focused on improving patient access through standardized process platforms, and those with autologous cell therapies in their pipeline are at work on decentralized approaches that could cut days from the typical manufacturing timeline. These aren't aspirational goals—they're established strategies that are already driving the decision-making process inside the research labs of sophisticated, forward-thinking cell therapy innovators.

Gene therapy manufacturing comes of age:

Commercial-scale manufacturing is imminent. Are gene therapy innovators ready?

By: Devin Hersey and Peter Walters

Section 4

Gradually, and then suddenly.

When Ernest Hemingway wrote those words in *The Sun Also Rises*, he couldn't have known about the gene therapy revolution that would follow nearly a century later—and yet he described it perfectly.

Sixteen years gradually elapsed between the first draft of the human genome and the first FDA-approved in vivo gene therapy. And now—suddenly—the FDA expects to approve 10 to 20 cell and gene therapy products a year. Decades of research have brought us to this moment, and very soon gene therapies will be a mainstay of commercial-scale biotech manufacturing.

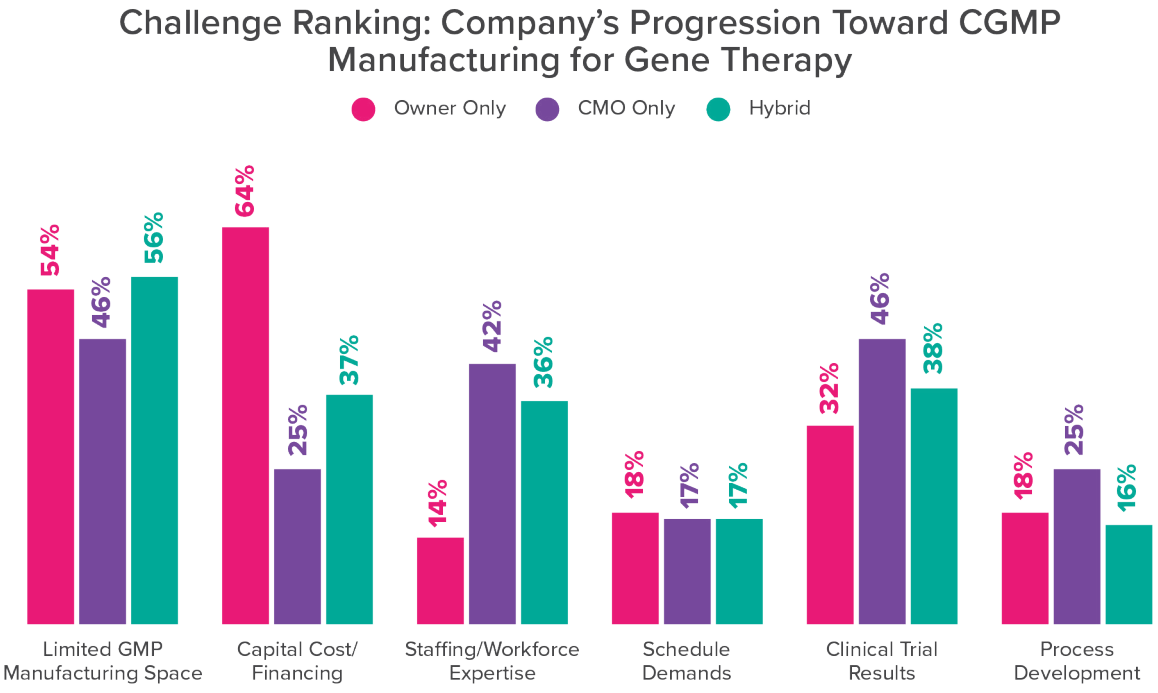
How are today's gene therapy manufacturers preparing for this step change, and what barriers stand between their breakthrough work at the bench and the patients who need their products at the bedside? Nearly half of all the *Horizons* survey respondents are at work in this field, so we asked them. Their answers paint the picture of a submarket that's rapidly maturing as researchers get comfortable pushing boundaries, developing and integrating new technologies, and laying the groundwork for future scalability.

TOP CHALLENGES IN GENE THERAPY RESEARCH:

1. Cleanroom space
2. Financial capital
3. Clinical results

FIGURE 4.1

Rank the following potential challenges in order of the most substantial to least substantial challenge for your company's progression toward CGMP manufacturing for gene therapy. (Rank order)



Source: CRB

Cell and gene therapies are often mentioned in the same breath, but there's good reason to distinguish them from a manufacturing perspective. For one thing, the gene therapy submarket is uniquely versatile—it can deliver a standalone drug product, or it can influence cell therapy programs as a critical ingredient. It's also replete with diverse sub-submarkets. In vivo gene editing, for example, has rapidly matured from a futuristic fantasy to a real-world possibility, with technologies like CRISPR driving progress and attracting investors. Today, companies active in gene editing account for 45% of all gene therapy financing.

Within this exciting context, we set out to understand what keeps gene therapy innovators awake at night as they prepare for CGMP manufacturing (Figure 4.1). Three challenges in particular caught our attention:

- **Limited CGMP manufacturing space:** Manufacturers are grappling with this chronic problem across the life science industry. Gene therapy innovators may feel its pinch especially hard, given that most are in early research phases and likely don't have their own manufacturing facility. Many lean on CMOs for outsourced capacity planning, who are heavily bottlenecked as a result.

- **Capital cost/financing:** As a whole, the gene therapy submarket raised $10.6B in venture funding last year, marking a 14% year-over-year increase. And yet as Figure 4.1 shows, project owners see financing as a much greater challenge than CMOs.

  Perhaps this is because CMOs generally operate under a different business framework. They have their own facilities but not their own products; instead of facing pressure to finance clinical trials, build infrastructure, and prepare for commercial launch, they're focused on delivering scheduled batches and maintaining a full backlog of manufacturing.

14%

year-over-year increase in gene therapy venture funding

- **Clinical trial results:** We were surprised that this challenge didn't rank higher. Strong trial results generate funding, which pays for manufacturing space, which in turn enables larger production volumes to supply further trials—and so the wheel of gene therapy turns, with clinical trials at its hub.

  It makes sense that CMOs would worry more than anyone else about this variable, because their manufacturing backlog depends on producing escalating volumes of an owner's product—which in turn depends on the outcome of clinical trials.

  Of course, owners are impacted the most, especially in a climate in which regulators approach gene therapies with appropriate caution. To edge toward commercial approval, owners need clinical trial results that will persuade regulators of their product's safety and unique therapeutic efficacy; if the market already offers a comparable product, approval is unlikely. Perhaps owners consider this such an obvious factor in their success that they chose to focus on other concerns when responding to this question.

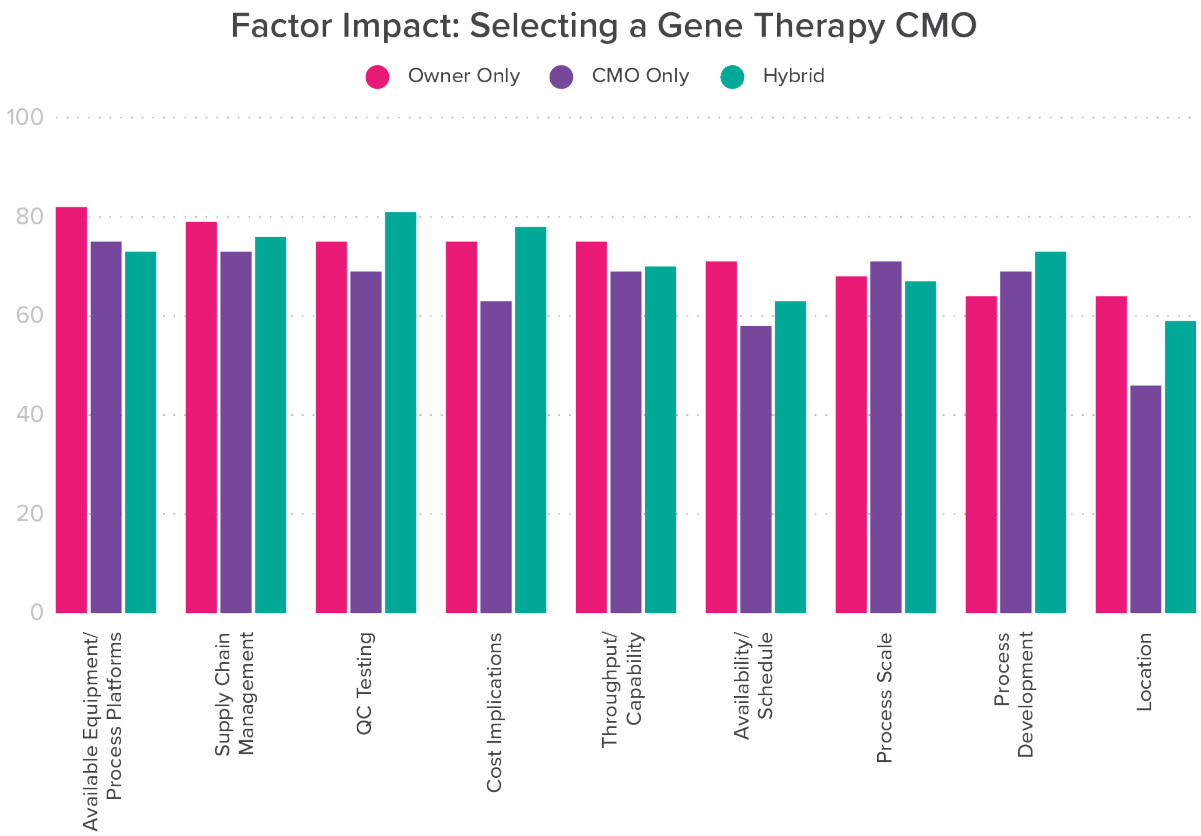
Though CMOs and owners experience many of these challenges differently, they do share one thing: a dependence on each other. Across the life science industry, but particularly in the nascent space of gene therapy manufacturing, the CMO-owner relationship is often a key to future success—which means it warrants a close examination.

HOW GENE THERAPY MANUFACTURERS EVALUATE POTENTIAL CMOS

We asked both owners and third-party manufacturers in the gene therapy submarket about the factors they consider most important when selecting or acting as a CMO. As it turns out, nearly everything is important; these "flat" results indicate an intensity of competition at play in today's gene therapy manufacturing environment (Figure 4.2).

FIGURE 4.2

How impactful are the following factors for selecting a gene therapy CMO or acting as a CMO? (Multiple choice)



Source: CRB

CMOs may find it useful to mine these results for opportunities to differentiate their service offering. In particular:

- **Available equipment/process platforms:** As the research pipeline matures and owners move closer to product launch, standardized manufacturing platforms with the potential to support rapid gene therapy production at the commercial scale are maturing, too. Contract manufacturers should proactively align their process capabilities with these emerging technologies; this will attract owners who need a manufacturing partner who can accelerate them to market with an effective and scalable platform.
- **Supply chain management:** This is a shared pain point for everyone. CMOs could distinguish themselves by, say, stocking several months' worth of single-use components, or by expanding their manufacturing capabilities to include plasmids (more on that later).

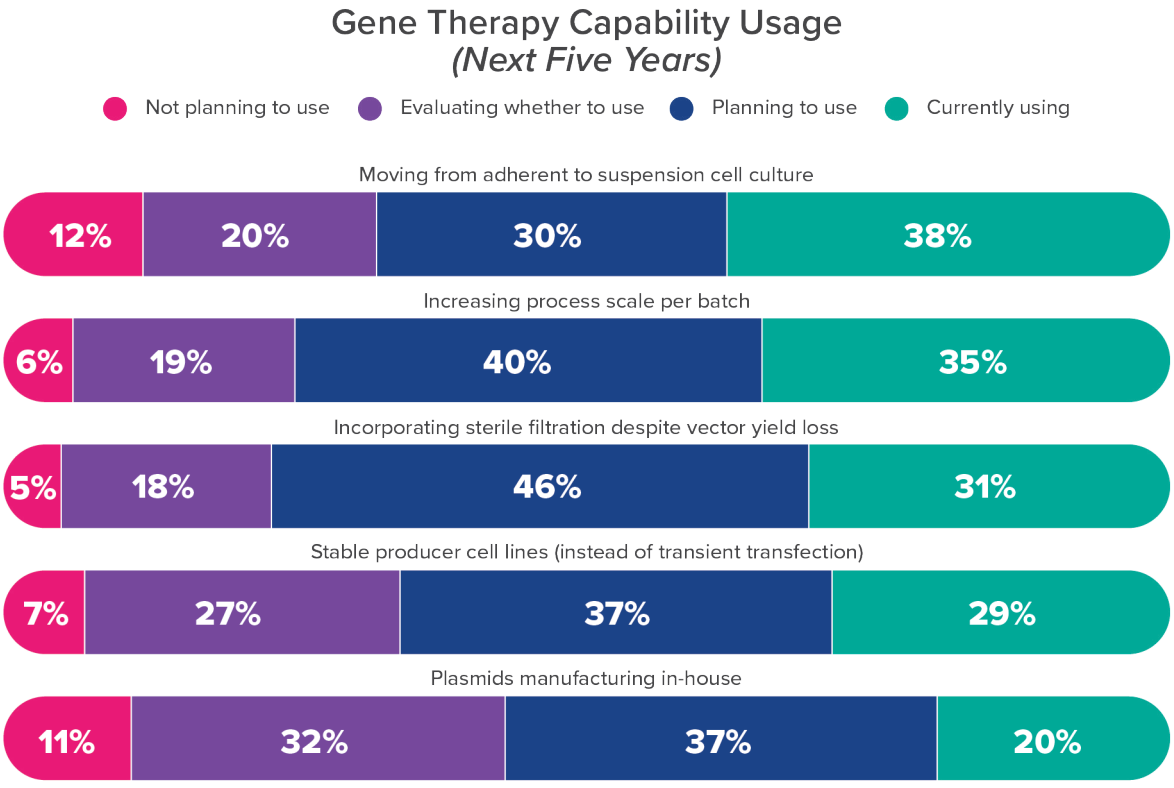
- **QC testing:** Of all the operations along the manufacturing lifecycle, owners very often seek to outsource this one. By expanding their QC testing capabilities, CMOs may find themselves in an advantageous position both as a resource and as a potential turnkey partner for companies.

THE KEYS TO COMMERCIALIZATION: SCALABLE, NEXT-GEN CAPABILITIES

Whether CMO or owner, what are gene therapy innovators doing right now to prepare for the larger scales they'll need to meet commercial demand in the future? To answer that question, we showed respondents a set of promising capabilities and asked them which ones they're currently using or planning to use in the near future (Figure 4.3).

FIGURE 4.3

Is your company currently using or planning on using the following gene therapy capabilities in the next five years? (Multiple choice)



Source: CRB

Each of these capabilities has the potential to dramatically improve the efficiency and scalability of gene therapy manufacturing. To make them work, companies will need to invest heavily in R&D, and they will need to investigate the facility and regulatory implications of integrating these forthcoming capabilities.

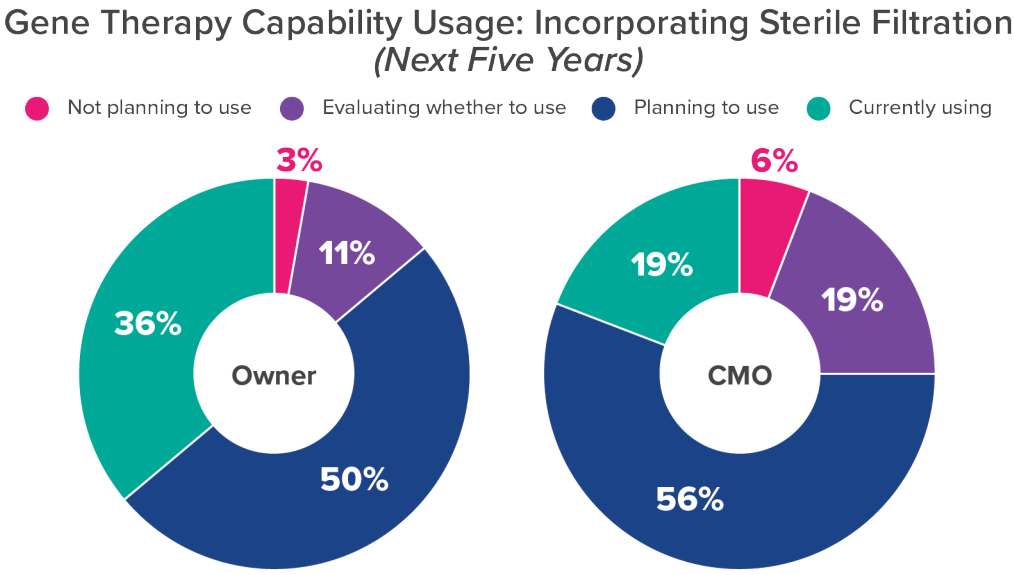
Despite these hurdles, our survey data shows strong momentum behind each of these capabilities—an encouraging sight for a submarket that's only just outgrowing its infancy and learning to run.

STERILE FILTRATION

Sterile filtration, a well-established tool in drug substance manufacturing, could unlock huge advantages for gene therapy manufacturers such as smaller and more efficient facilities, lower operating costs, and opportunities for process closure. There's a significant potential drawback, though: lentiviral and retroviral vectors typically sustain significant yield loss when exposed to a sterile filter.

FIGURE 4.4

Is your company currently using or planning on using the following gene therapy capabilities in the next five years? (Multiple choice)



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This is likely why only about a third of owners and even fewer CMOs in our survey are currently using a sterile filter. As long as they're manufacturing small batches of viral vector to support pre-clinical or early clinical research, a biosafety cabinet can maintain the necessary sterile processing boundary—without impacting yield.

To transition that benchtop process into a commercial-scale CGMP facility, though, companies would have to meet the regulatory requirements for aseptic processing. That means taking the level of aseptic processing that's typically reserved for a fill-finish step and applying it across the entire process train—an onerous prospect from the perspective of validation, equipment selection, and cost. Even if a manufacturer could somehow justify this approach in the boardroom, they may find it impossible in the plant; many of the technologies used for larger-scale manufacturing, like chromatography systems, were not designed to support aseptic processing.

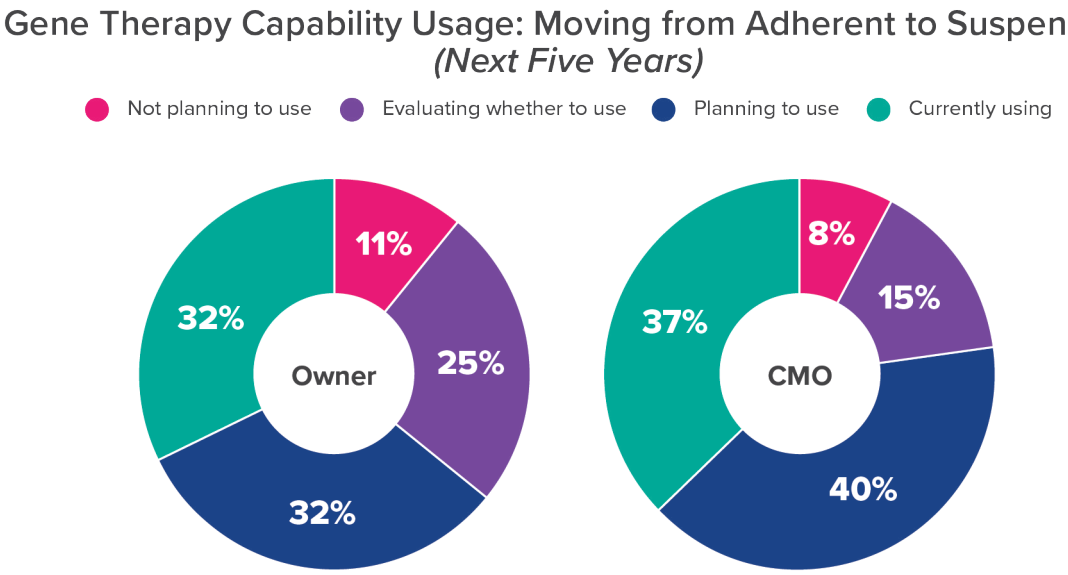
This is likely driving the large segment of owners and CMOs who are planning to incorporate sterile filtration in the future. To make it work, they'll have to either optimize the process to minimize loss or build that yield loss into their scalability strategy and plan their product train around it.

It's interesting to note that CMOs are less likely than owners to use sterile filtration in their current approach, but slightly more likely to be planning for (or evaluating) its adoption. It could be that CMOs have historically avoided sterile filtration because they're focused on maximizing their small-batch yields; meanwhile, they've seen owners jump ahead with adoption, which may have recently incentivized them to catch up.

MOVING FROM ADHERENT TO SUSPENSION CELL LINES

FIGURE 4.5

Is your company currently using or planning on using the following gene therapy capabilities in the next five years? (Multiple choice)



Source: CRB

Adherent cell lines, which use an anchor point like tissue or a mesh surface to reproduce, require substantial surface area, a lot of operators to perform cell washing and expansion operations, and the potential for extensive open processing.

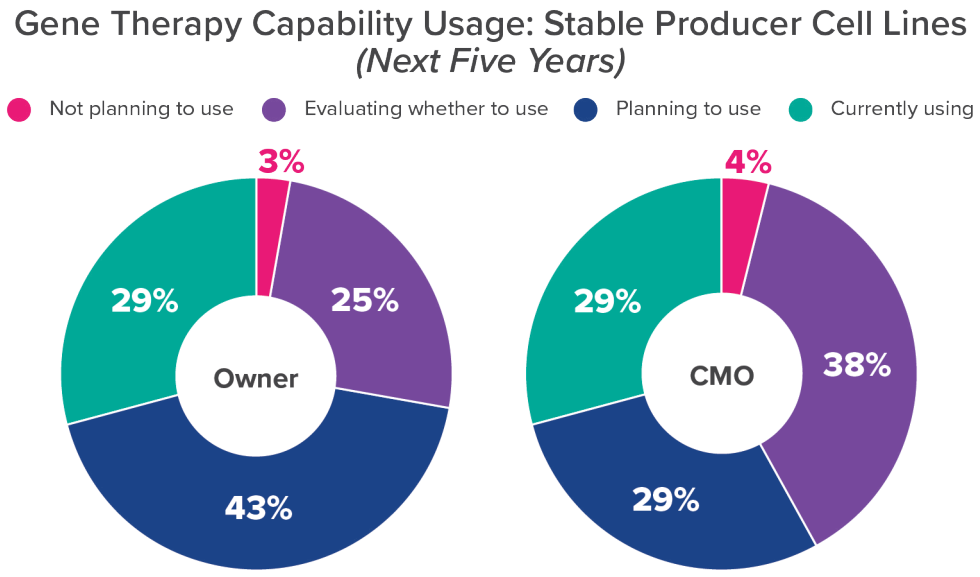
Many of our respondents have moved away from these challenges by transitioning to suspension cell cultures, which allow for a denser use of operational space while paving the way for closed and automated processing. There is also the advantage of familiarity: gene therapy manufacturers can borrow from the playbook of therapeutic protein manufacturers, who leveraged this approach to leap from benchtop to commercial production 30 years ago.

STABLE PRODUCER CELL LINES (INSTEAD OF TRANSIENT TRANSFECTION)

Though it's currently a more established technology than stable producer cell lines, transient transfection is a tricky approach to maintain as production quantities grow. It requires large volumes of raw transgene material, which drives up costs, and it depends on complex chemical dynamics within the bioreactor. If manufacturers pursue transient transfection all the way into commercial production, they'll find themselves stuck with limited efficiency and high production costs, and they'll be handcuffed to a transgene supply chain that's struggling to meet demands.

FIGURE 4.6

Is your company currently using or planning on using the following gene therapy capabilities in the next five years? (Multiple choice)



Source: CRB

In contrast, a highly productive bank of stable producer cells offers the potential for a more efficient, cost-effective, and scalable process. We haven't yet seen this technology fully deployed, but the general concept looks a lot like classic biotech: as manufacturers grow a cell line, they can grow the transgene element at the same time.

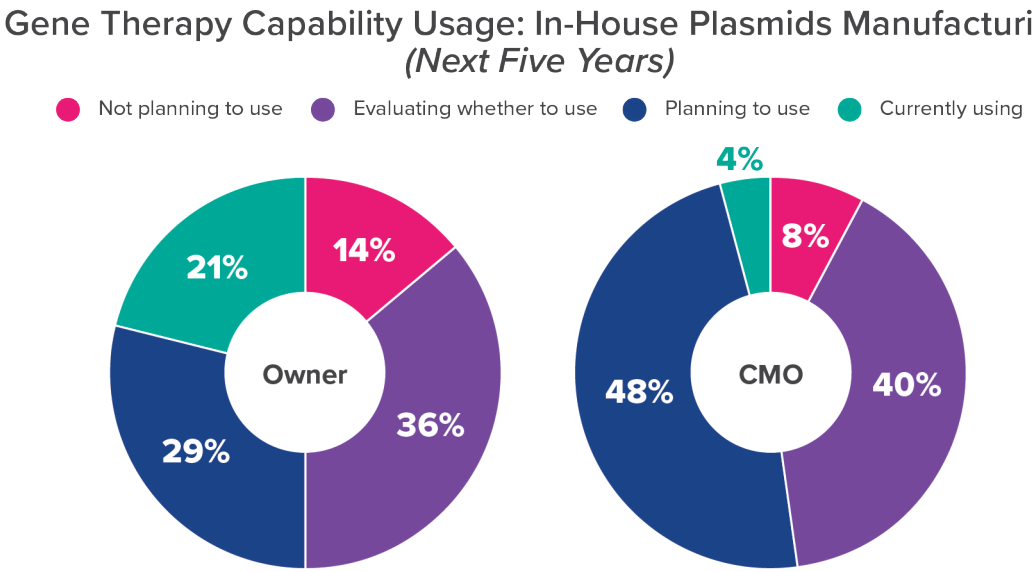
Before this approach becomes a mainstay of gene therapy manufacturing, though, companies need to work out how to engineer cells capable of making the vector without being transfected at scale. CMOs appear to be leading this R&D effort; although owners are currently more likely to have stable cell lines in place already, nearly 90% of CMOs are either planning to adopt this approach or are actively evaluating its potential as a gateway to greater scalability. The small number of CMOs with a stable cell line currently available are ahead of the curve; this is likely a strategic component of their position as a commercial-ready turnkey partner.

PLASMIDS MANUFACTURING IN-HOUSE

Only a handful of companies around the world are capable of manufacturing this critical raw material, which has led to a chronic bottleneck in the supply chain.

FIGURE 4.7

Is your company currently using or planning on using the following gene therapy capabilities in the next five years? (Multiple choice)



Source: CRB

This is likely why our respondents are showing keen interest in bringing their plasmids source in-house. It's a complex proposition that will take a lot of R&D to pull off, but the promise of controlling the availability, quality, and cost of such critical materials is a strong incentive.

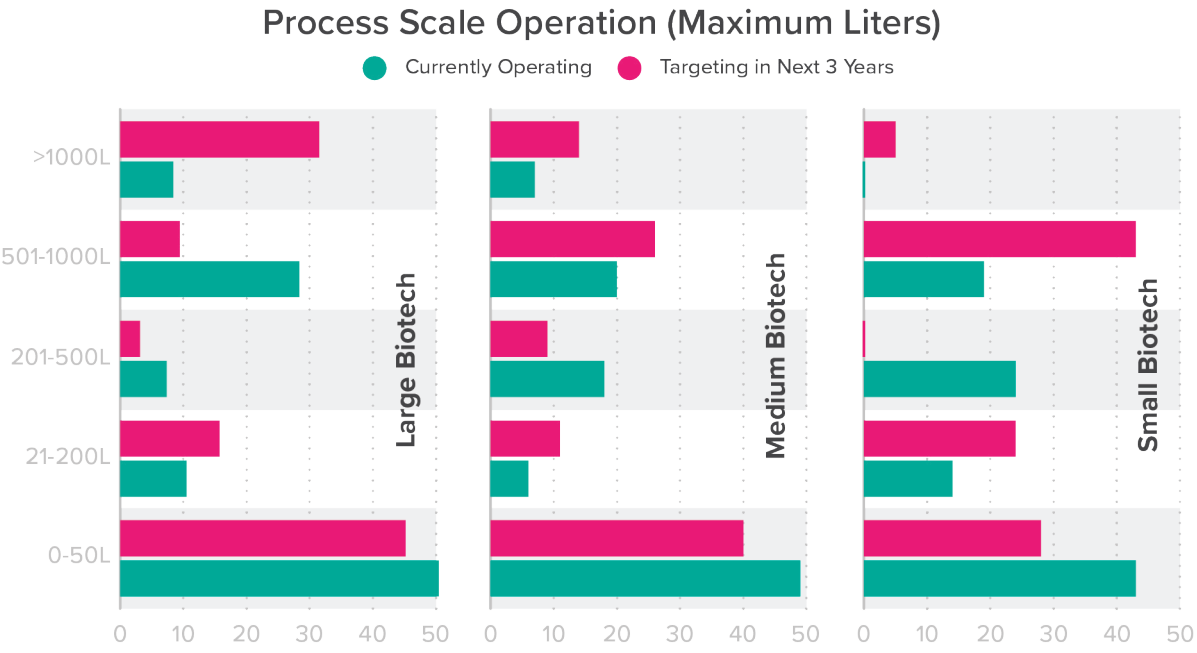
For CMOs, this trend could be game-changing. As the data shows, few are currently manufacturing plasmids, though interest is high. Those who add this capability in the future could find themselves at a great competitive advantage.

WHAT DOES PROCESS SCALABILITY LOOK LIKE FOR GENE THERAPY MANUFACTURERS?

There's a reason why the emerging capabilities described above are attracting so much attention among our survey respondents. Change is coming rapidly to this submarket, and gene therapy researchers are under pressure to change with it.

FIGURE 4.8

What process scale (i.e., maximum bioreactor size) does your company currently operate for gene therapy manufacturing? What process scale is your company targeting in the next three years? (Open entry)



Source: CRB

Whether well-established or just starting up, most companies with their hand in gene therapy research today are producing the small-scale batches necessary to support pre-clinical or early clinical trials; even early phase cell therapy studies that rely on a gene therapy component aren't likely to require large batches of critical material.

This picture of small-scale benchtop manufacturing speaks to the infancy of the gene therapy industry. But as we can see in Figure 4.8, most respondents expect to increase their production volumes sharply within the next three years. Large biotech companies are especially aspirational in their processing goals, perhaps because they can leverage existing infrastructure to accelerate scale-up—or perhaps they're more likely to target indications with a large patient population, as opposed to rare or orphan diseases with a smaller market attached.

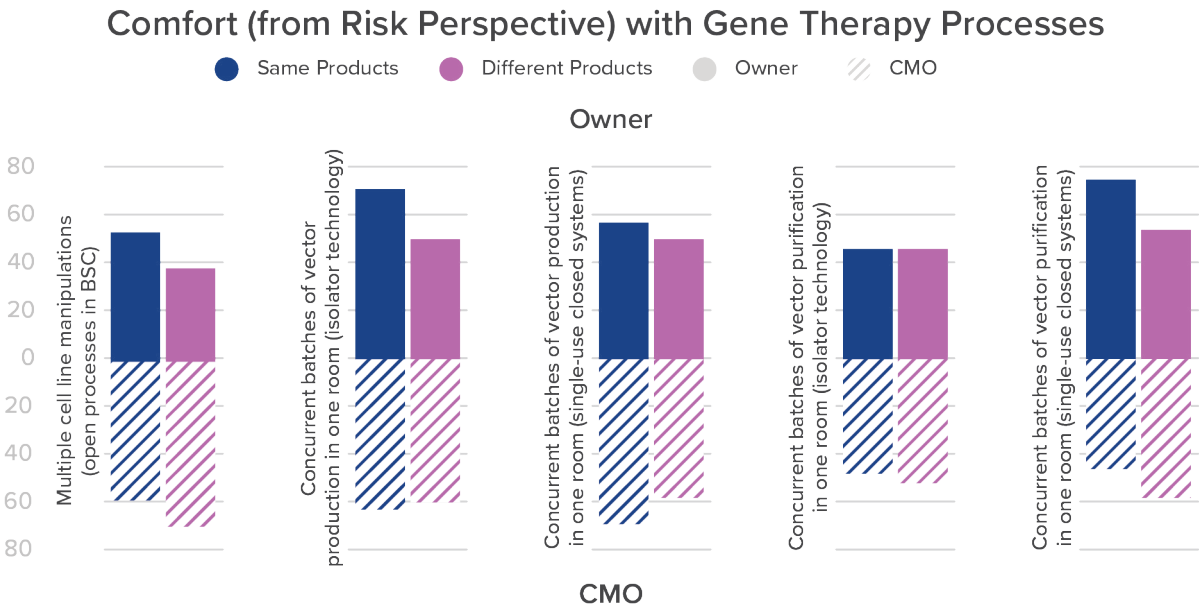
Some of the respondents represented in Figure 4.8 will force their way up that Y-axis using established approaches such as transient transfection, but those who invest early in more innovative and scalable capabilities will find themselves better prepared to enter the commercial marketplace.

COMPLIANCE WITH SCIENCE: HOW GENE THERAPY MANUFACTURERS APPROACH RISK

Commercial-scale gene therapy manufacturing requires careful risk assessment and a production approach that balances efficiency with quality and control. Finding that balance isn't easy—and maintaining it to the satisfaction of a cautious regulatory body can be even more difficult.

FIGURE 4.9

For concurrent gene therapy processes with either different batches of the same product, or different batches of different products (but same modality), would you be comfortable from a risk perspective with the following? (Yes/No)



Source: CRB

From that point of view, we were surprised to see that most respondents reported relatively high comfort with vector production. This could reflect the makeup of our survey audience: as we've noted, most respondents are in early R&D and process development roles, which means they're operating upstream of the stringent quality programs that govern CGMP manufacturing.

It's possible that such high levels of comfort could survive a shift out of the lab and into the commercial-scale plant, though it's unlikely to happen quickly; manufacturing viral vectors for different products in the same room, while perhaps scientifically possible and ideal in terms of efficient throughput, may be difficult to justify from a regulatory perspective without prohibitively rigorous risk management and a matching quality program in place.

Within this big picture, we found two interesting nuances worth noting:

- **Isolators are slightly more attractive than single-use technologies (SUTs).** This may come down to the attitude that single-use components mean elevated risk; manufacturers may worry that plastic components could wear down, for example, or that a faulty connection could precipitate a leak. Isolators, on the other hand, are a validated containment system. For high-risk operations, respondents may choose to take on the extra expense of isolator technology.

  This attitude will likely shift over the coming decade as manufacturers and regulators grow more accustomed to SUTs in gene therapy production, which will enable greater flexibility and faster product changeovers.

- **CMOs have a higher risk tolerance than owners.** Because they are familiar with the practice of managing multiple clients within the same facility, CMOs may already have the controls and validation in place to comfortably mitigate the risks of switching between products. This could explain why, on the whole, they responded more favorably than owners in terms of risk tolerance.

The bottled potential of gene therapy is about to explode

For patients awaiting a cure—and for manufacturers racing to reach the market—the journey to effective and accessible gene therapies may have felt long. In the background, though, a momentous shift is taking place, and quickly.

Scalable technologies like stable producer cell lines are emerging; attitudes toward the risks and rewards of efficient gene therapy manufacturing are shifting; innovators are laying the groundwork for tailored commercial approaches that will help them succeed in the marketplace. As a result, today's gene therapy manufacturers are set to transform the lives of millions of patients—gradually, and then suddenly.

Transformative changes in therapeutic protein manufacturing:

A close look at the trends and technologies shaping a rapidly evolving industry

By: Rob Boulanger and John Rubero

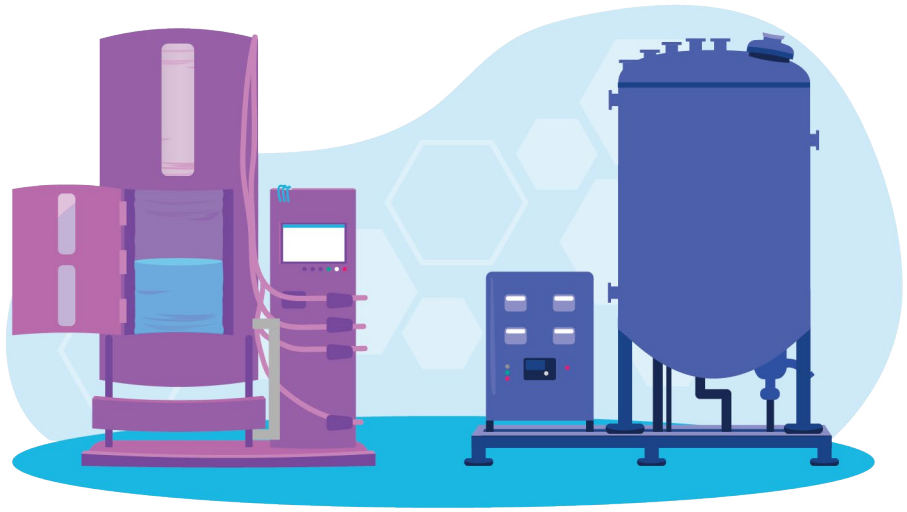
Section 5

Last year was a milestone year for therapeutic proteins, and not only because the US Food and Drug Administration (FDA) approved the 100th antibody therapy on the market. It marked the centennial anniversary of the discovery of insulin, the world's first treatment for diabetes, and also the first therapeutic protein. In 1921, when insulin therapy was discovered, there was no genetic engineering involved. It was a long road from there (60 years!) until the first recombinant protein therapeutic, Humulin (human insulin) was introduced in 1982, and the field of therapeutic proteins began to take its current shape—a fast-evolving industry adjusting to a variety of advanced technologies for the treatment of diseases from diabetes to cancer, infectious diseases, and many more.

And now, 100 years since insulin started saving lives, we have leveraged therapeutic proteins to combat the COVID-19 pandemic. Monoclonal antibodies (mAbs), in particular, shared center stage with vaccines during the height of the pandemic. While cell and gene therapy innovations are generating a particular kind of frontier excitement these days, therapeutic protein manufacturing remains a champion of innovation—and in fact, may just be finding their stride.

With our *Horizons* survey, we were able to probe into some of the hot-button areas in the therapeutic protein industry, ranging from the types of mAbs trending in clinical pipelines, to factors driving the use of stainless-steel vs. single-use technologies, and changing perceptions associated with process closure. The following insights, collected from more than 300 therapeutic protein researchers and manufacturers

across the United States and Europe, will illuminate what leaders in this industry are investing in today and where that investment may take them tomorrow.



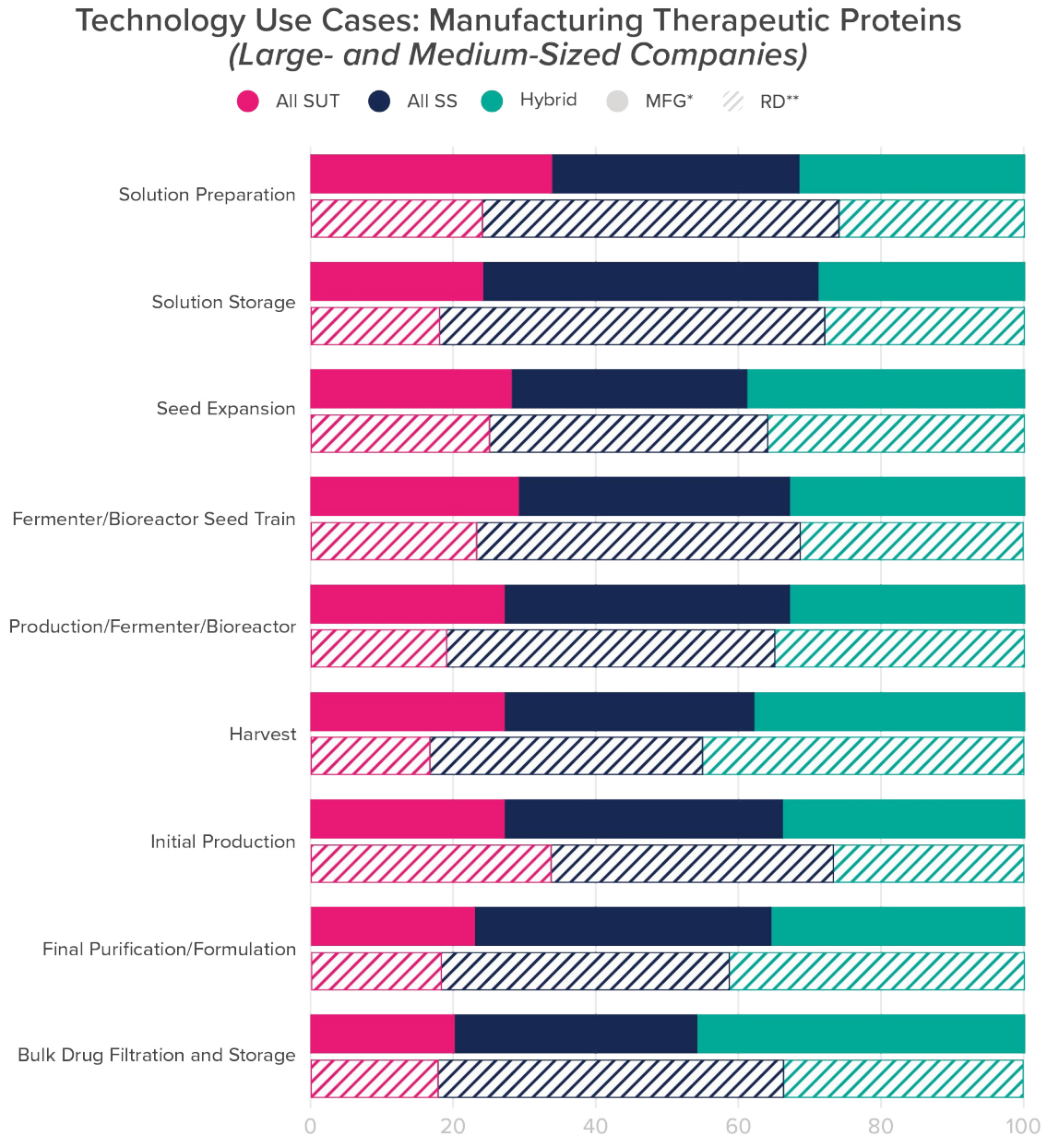
STAINLESS STEEL VS. SINGLE-USE TECHNOLOGY

Stainless-steel (SS) equipment and infrastructure have a long history in life science manufacturing, generally tracking with the demand for high quality and throughput of therapeutic drug products. In contrast, single-use technologies (SUT), such as disposable cell culture bioreactors, are a relatively recent innovation. They entered CGMP manufacturing with a bang, making a huge impact due to the benefits of rapid product changeover, reduced capital cost, and reduced cleaning and sanitization requirements. These technologies are not a magic bullet, though, and debate about which technology—SS or SUT—will better serve manufacturing needs in the future is ongoing. Most companies tend to emphasize either fixed SS infrastructure or SUT based on their scale of operation (i.e., clinical or commercial scale), product pipeline, and business goals (i.e., integrated manufacturing company, contract manufacturing organization, or both)—and some companies are reaping the benefits of both worlds by using a hybrid approach.

Interestingly, our respondent data shows that the SS approach is currently adopted by the largest percentage of users overall, signaling perhaps a “renaissance” of SS use, which dominated traditional manufacturing prior to the late 1990s (Figure 5.1). This could be a nod to the ever-growing need for large-scale therapeutic protein production, which for traditional batch processes we would consider above the 2,000 L-scale for production bioreactors. Large-scale manufacturing for commercial production has tended toward large, fixed SS infrastructure in the past, partly due to legacy facilities built to meet large market demand before the onset of SUT, while clinical manufacturing is much more likely to favor SUT, since only a small amount of product is required. Along these lines, companies with a broad pipeline generate many different product candidates, and thus, benefit from quick changeover capabilities.

FIGURE 5.1

Where does your organization primarily leverage single-use technology (SUT), stainless-steel (SS) infrastructure, or a hybrid of SUT and SS technology to manufacture therapeutic proteins? (Multiple choice)

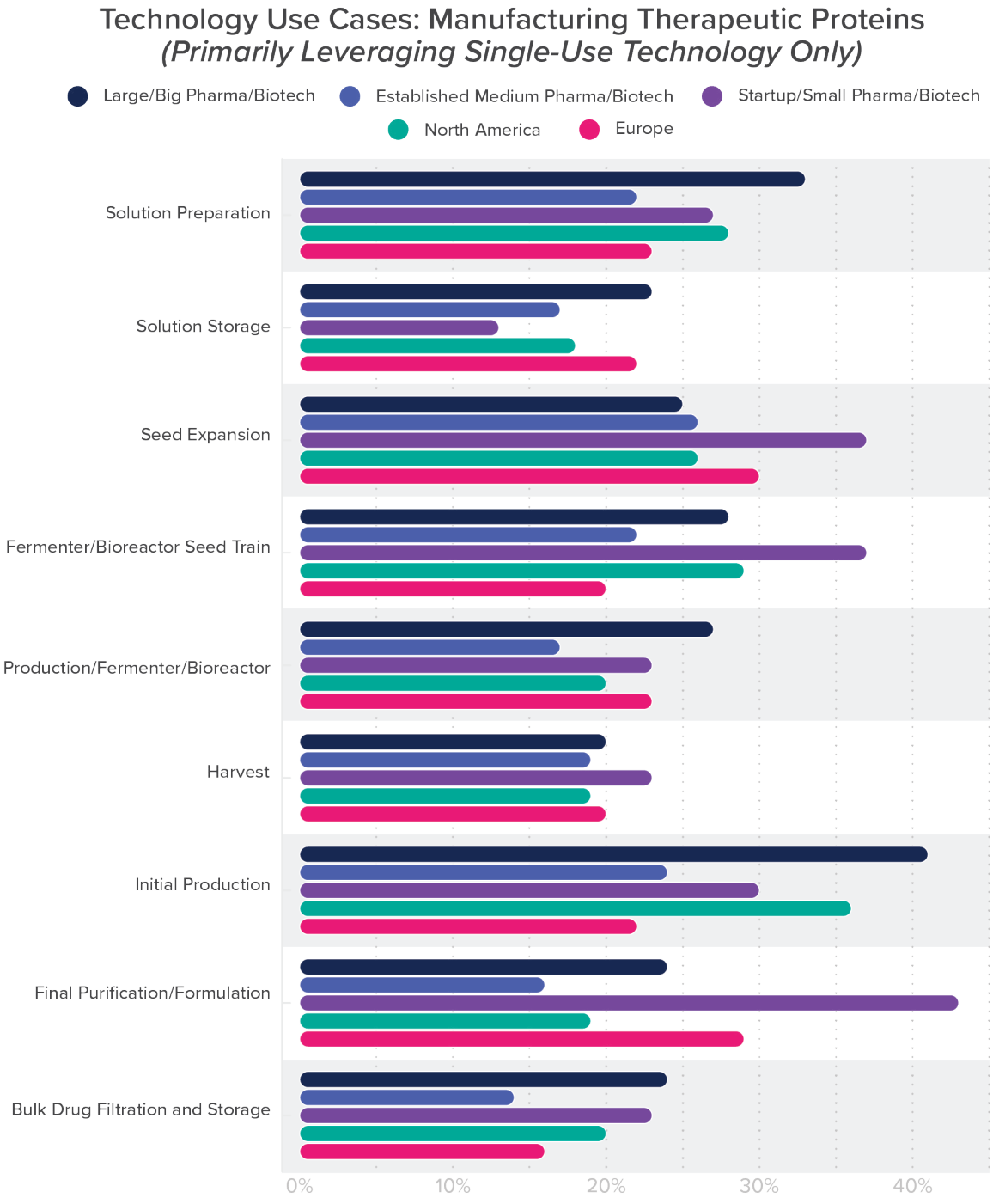


**Roles of process/product development, clinical manufacturing, engineering/facilities, capital projects, commercial manufacturing*
***Roles of clinical research, discovery and research, pre-clinical development, and translational R&D*

Source: CRB

FIGURE 5.2

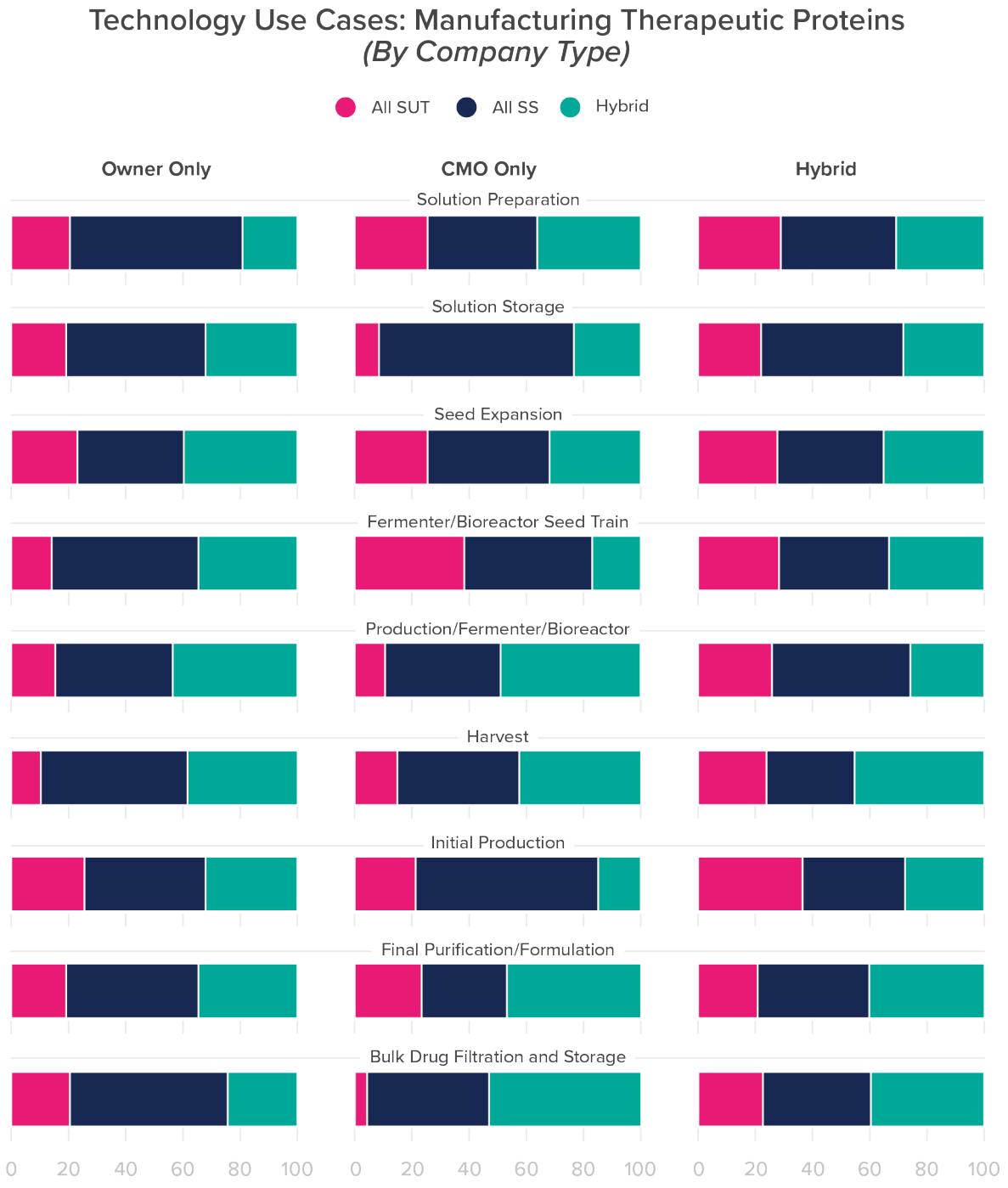
Where does your organization primarily leverage single-use technology (SUT), stainless-steel (SS) infrastructure, or a hybrid of SUT and SS technology to manufacture therapeutic proteins? (Multiple choice)



Source: CRB

FIGURE 5.3

Where does your organization primarily leverage single-use technology (SUT), stainless-steel (SS) infrastructure, or a hybrid of SUT and SS technology to manufacture therapeutic proteins? (Multiple choice)

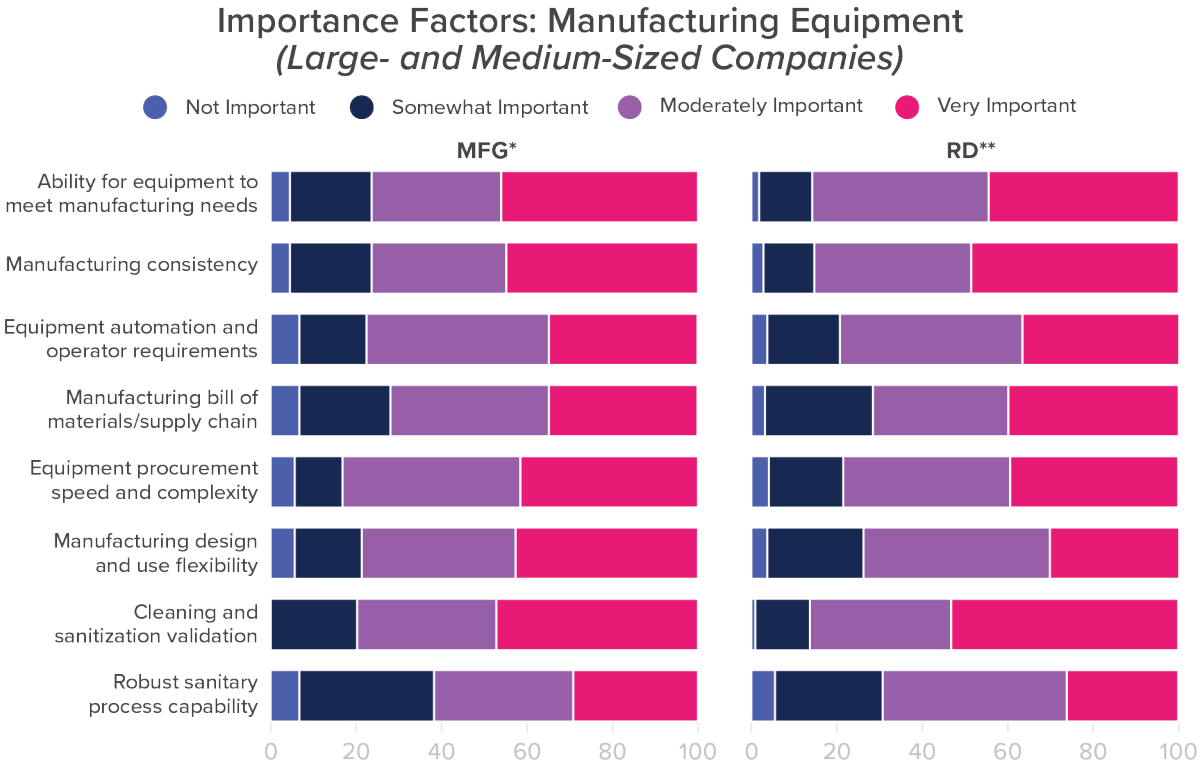


Source: CRB

SUTs are still the equipment type of choice for most small pharma/biotech companies and contract manufacturing organizations (CMOs). This makes sense for smaller companies who possess little or no experience with SS infrastructure. Application of SUT obviates the need for clean-in-place (CIP) and sterilization-in-place (SIP) procedures, reducing validation costs and the need for expensive utility systems. Thus, an SUT-centric manufacturing philosophy may be best for small companies on tight budgets. For CMOs, who are all about speed in transitioning from one campaign to the next, quick product changeovers are critical and a big driver for the use of SUTs. As mentioned above, SUTs do not need cleaning and sanitization steps typically required of fixed SS equipment; as a result, the need for validation of CIP and SIP operations is eliminated. They are an extremely attractive option for companies emphasizing either small-scale batch operations or intensified processes, which are designed to increase product throughput while maintaining a scale of operation amenable to application of SUT (process intensification is addressed in greater detail in the following section).

FIGURE 5.4

Rate the importance of each factor driving your organization's preferred approach toward using SUT and/or SS equipment for manufacturing of therapeutic proteins. (Multiple choice)



**Roles of process/product development, clinical manufacturing, engineering/facilities, capital projects, commercial manufacturing*
***Roles of clinical research, discovery and research, pre-clinical development, and translational R&D*

Source: CRB

Companies with needs oscillating between the two ends of “All-SS” and “All-SUT” are often seen adopting hybrid approaches. A typical example of a hybrid approach may be found in the harvest step, where a centrifuge is generally limited to SS fabrication, while centrate clarification filters are widely available as single-use equipment. Another example would be a case where seed expansion might be performed using SUT (e.g., single-use spinner flasks and/or benchtop bioreactors mounted on rocker platforms), while larger N-1 and/or N production bioreactors consist of fixed SS equipment.

Manufacturers have started to look at hybrid approaches based on a desire to reduce bioburden or cross-contamination risk in specific process steps. Additionally, process intensification efforts typically lead to smaller scale operations, which open new doors to SUT application. So, while larger companies with larger footprints may lean towards larger SS systems, they may also consider SUTs for a few steps in between, such as seed expansion and harvest, as they focus on intensification.

IMPLICATIONS FOR PROCESS INTENSIFICATION

We expect the percentage of large companies using SUTs to increase in the future, given that process intensification has gained interest as a means of improving manufacturing efficiency. The basic goal of an “intensified” process is to achieve the productivity of a conventional batch process, but with a much smaller scale of operation. Essentially, this is achieved by increasing the specific productivity of the process (e.g., higher throughput per unit volume of cell culture and/or liquid chromatography resin).

In upstream manufacturing, intensification might entail operation of a continuous N production cell culture bioreactor, for example, or be achieved by increasing cell densities in a batch-process N-1 seed bioreactor. In the realm of downstream purification, intensification typically means making both individual unit operations and the overall sequence of connected purification steps, as continuous as possible. For example, a continuous liquid chromatography process allows packed column volumes to be reduced significantly, making single-use columns feasible.

This upward trend toward SUT usage is evident when considering the example of an intensified batch cell culture process, where higher cell densities at the N-1 seed culture stage equate to higher product titers in the subsequent N production bioreactor. With an intensified upstream batch process, product titers of 10 g/L or more are currently achievable. Assuming a level of productivity of 10 g/L, a 2,000 L single-use production bioreactor provides the same throughput as a 10,000 L SS bioreactor operating at a product concentration of 2 g/L.

With respect to downstream purification, process intensification also equates to a smaller equipment outlay and higher specific productivity. However, the tradeoffs of a fully continuous downstream process include increased automation complexity and potential repercussions associated with process “upsets.” Therefore, while continuous sequences of unit operations are possible, including steps such as

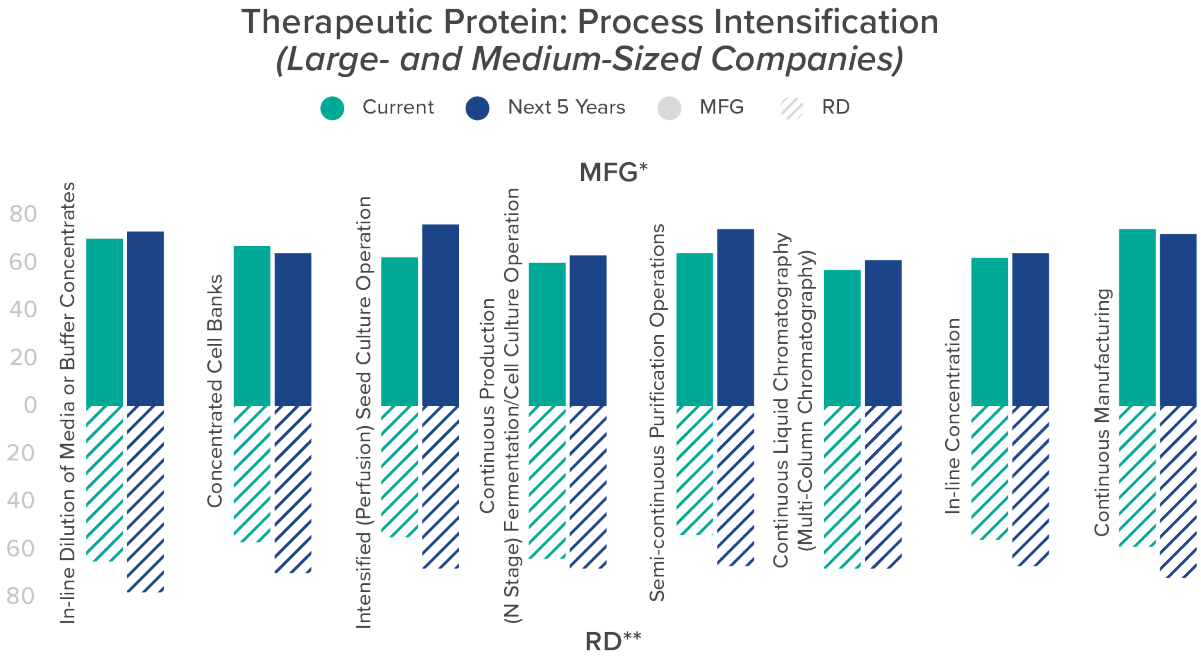
virus inactivation, ultrafiltration, and diafiltration, semi-continuous approaches to downstream manufacturing have been more prevalent to date.

Trends also appear to indicate movement toward completely continuous downstream purification platforms and increased application of SUT in downstream processing. For example, in a continuous chromatography application, manufacturers can substitute a series of smaller SUT columns for a single, large SS column to eliminate column packing and column transport issues. Further, companies may look to "scale out" instead of scaling up their production processes, using standardized SUT platforms to create "seamless" transitions between late-stage clinical production and commercial manufacturing operations. However, it should also be noted that process intensification can be employed using fixed SS equipment, or a hybrid between SS and single-use equipment, retaining the efficiency gains associated with continuous operations.

According to our respondents, there seems to be increased interest in continuous processes across the board, both with R&D companies and those with focus on clinical and commercial manufacturing (Figure 5.5).

FIGURE 5.5

Is your company using or planning to use any of the following manufacturing technologies to aid in therapeutic protein process intensification? (Yes/No)



**Roles of process/product development, clinical manufacturing, engineering/facilities, capital projects, commercial manufacturing*
***Roles of clinical research, discovery and research, pre-clinical development, and translational R&D*

Source: CRB

HOW A CONTINUOUS DOWNSTREAM MANUFACTURING PROCESS CAN DRIVE DOWN THE COST OF GOODS

- Continuous downstream manufacturing processes make more efficient use of chromatography columns and resins
- Depending on resin binding capacity, continuous chromatography can reduce resin usage up to 40% compared with a conventional batch process
- Buffer usage may be reduced by approximately 30% to 35%, due to higher column loading rates associated with continuous operation
- Single-use columns that are prepacked and easy to handle/transport can be adopted
- As process intensification becomes more prevalent, application of SUT enters the realm of feasibility

Key Takeaway:

Process intensification is the wave of the future, and it promises to deliver improved manufacturing efficiency, streamlined facility design, and reduced cost of goods.

A PARADIGM SHIFT IN PROCESS CLOSURE DEFINITIONS

The definitions of "open" and "closed" processes in drug manufacturing have been refined somewhat since 2005. This was a watershed year for life science companies because of the introduction of some very important International Conference on Harmonization (ICH) guidelines, namely the ICH Q8 and Q9 guidelines, which mainly addressed principles of Quality by Design (QbD) and Quality Risk Management (QRM), as well as Process Analytical Technology (PAT) for real-time process monitoring.

Before these guidelines emerged, the definition of process closure was often rigidly defined as an aseptic system. For example, equipment involved in a production process had to be cleaned in place, steamed in place, and maintained under positive pressure in a highly classified cleanroom (i.e., Grade C). At that time, many manufacturers did not complete risk assessments to demonstrate that the contamination risks were adequately mitigated in their processes, and as a result, they were subject to more questions by quality auditors and regulators. Against this backdrop, companies tended to validate anything and everything, without much consideration of relative criticality. A huge amount of time, effort, and money went into validating all processes indiscriminately, which likely contributed to unnecessarily lengthening development timelines.

Enter the ICH Q8 and Q9 guidelines. The FDA emphasized through these guidelines that companies must focus on the process parameters critical to their product quality,

and ultimately, patient safety. The FDA expects companies to “know their process and understand their risk” and validate accordingly. The QbD principles in ICH Q8 were intended to help developers identify Critical Process Parameters (CPP) and Critical Quality Attributes (CQA) during process development. Naturally, with the focus now shifting to these critical parameters and an approach more suitable to mitigate risks, the definitions of process closure also saw changes that led to fewer restrictions, but more awareness and justification of processes. Open manipulations are still carefully scrutinized and the trend is to eliminate open processes, where possible, but it’s done based on a risk assessment. This ensures that important validation requirements are not missed, while eliminating unnecessary validations.

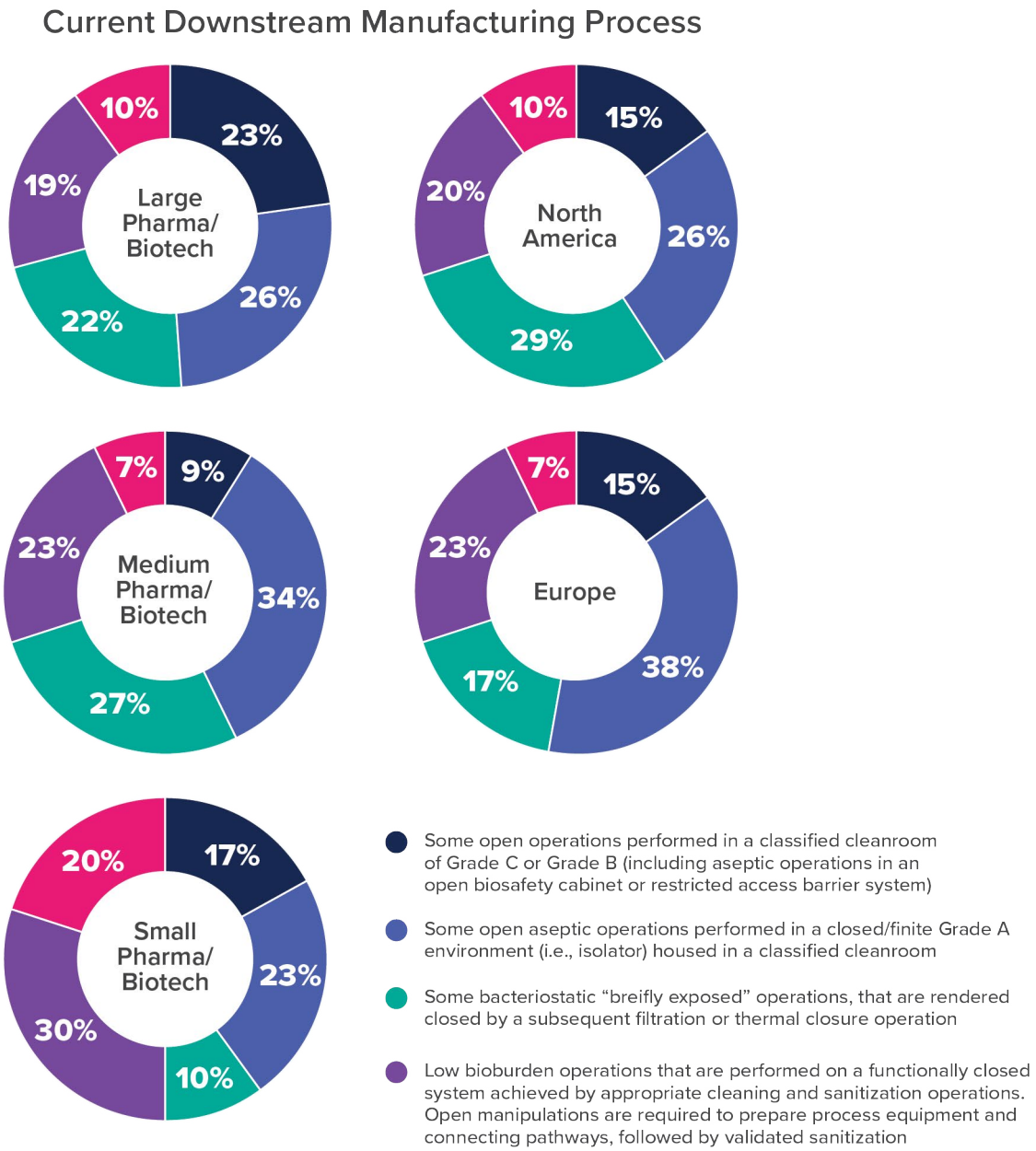
Low bioburden process closure operations were deemed acceptable when backed by a thorough risk assessment. For instance, it’s possible to convert open manipulations to a “closed” state with pre-use, non-caustic CIP water-for-injection (WFI) flushing in a controlled not classified space. This technique could provide a low bioburden starting point and ensure closure without having to resort to CIP, followed by SIP operations, in higher classification cleanrooms. Low bioburden operations are required to maintain a validated bacteriostatic state, but not required to be sterile. As such, this meets the FDA recommendation for developers to evaluate the contamination risk and mitigate appropriately. In addition to eliminating some fairly cumbersome process closure procedures, this also helps to create a more cost-efficient, lean process with a reduced carbon footprint. It may not be 100% bulletproof, but it will be well within the validated state and tolerated risk.

Our respondent data indicates that many manufacturers still utilize open processing, coupled with the implementation of quality principles according to ICH Q8 and Q9 (Figures 5.6 and 5.7). In general, most companies are at least aware of the ICH guidelines and are either considering the implementation of QbD and QRM or have already committed to it. We believe R&D respondents emphasized QbD more than their manufacturing counterparts, presumably because QbD originates from, and is driven by, process development.

A similar case can be made for PAT, as process development is typically focused on determining CPP. The PAT principle is recommended within ICH Q9 as a system for designing, analyzing, and controlling biomanufacturing more efficiently, with the goal of ensuring final product quality. This is done by online monitoring and measurement of CPPs and CQAs in real-time such that it facilitates improvements in process control, root cause analysis, and process characterization.

FIGURE 5.6

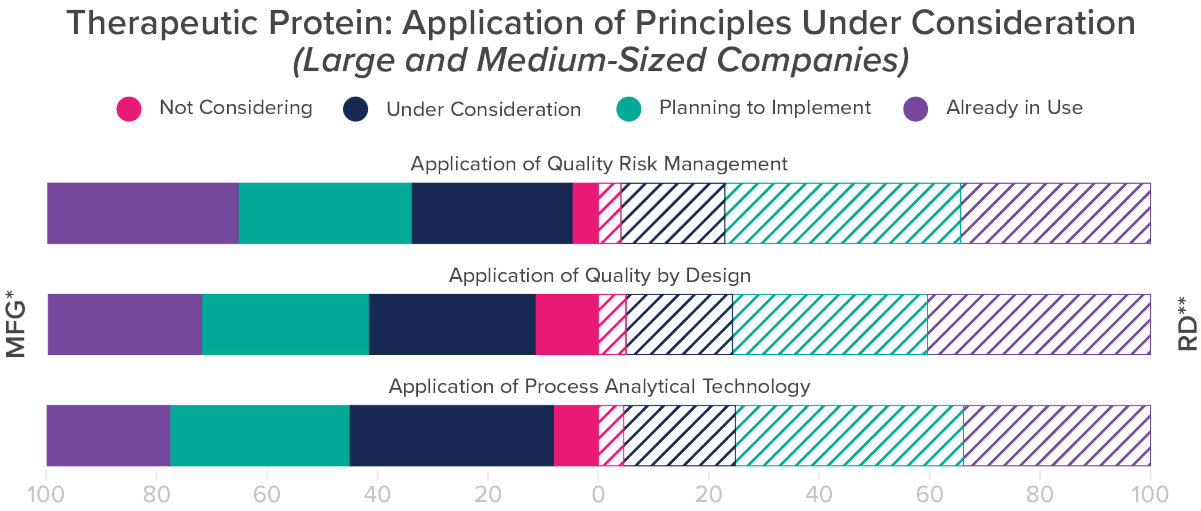
Which of the following best describes your current therapeutic protein downstream manufacturing process? (Select one)



Source: CRB

FIGURE 5.7

Are you currently implementing or considering implementing the following systems or principles in your therapeutic protein manufacturing operation? (Multiple choice)



**Roles of process/product development, clinical manufacturing, engineering/facilities, capital projects, commercial manufacturing*
***Roles of clinical research, discovery and research, pre-clinical development, and translational R&D*

Source: CRB

Respondent companies, and in general the entire industry, have embraced the idea that a process step doesn't have to be aseptic or sterile to be considered closed. Even with rigorous cleaning, air changes, proper gowning etc., the operators in the room still shed approximately 17,000 particles per minute—and many of these contain bacteria. Removing the manufacturing suite contaminants (by a validated procedure) and keeping the system closed while the product is processed is likely a lower risk scenario than open processing in a biosafety cabinet with a high-grade cleanroom. The critical thing is to ensure removal of potential contamination from the system, following process closure, to ensure a low bioburden condition.

Ultimately, a risk-based approach in establishing robust and practical process closure procedures is part of a manufacturing philosophy designed to ensure patient safety, product efficacy, and product availability. In addition, employing process closure methods that are germane to specific sanitary process requirements will help streamline validation requirements. Therefore, risk-based process closure should also help reduce manufacturing costs, and potentially, reduce overall timeline to market.

Key Takeaway:

Since 2005, the FDA has emphasized a risk-based approach to commissioning and qualification of biopharmaceutical processes—a paradigm shift heralded by the agency's ICH Q8 and Q9 guidelines.

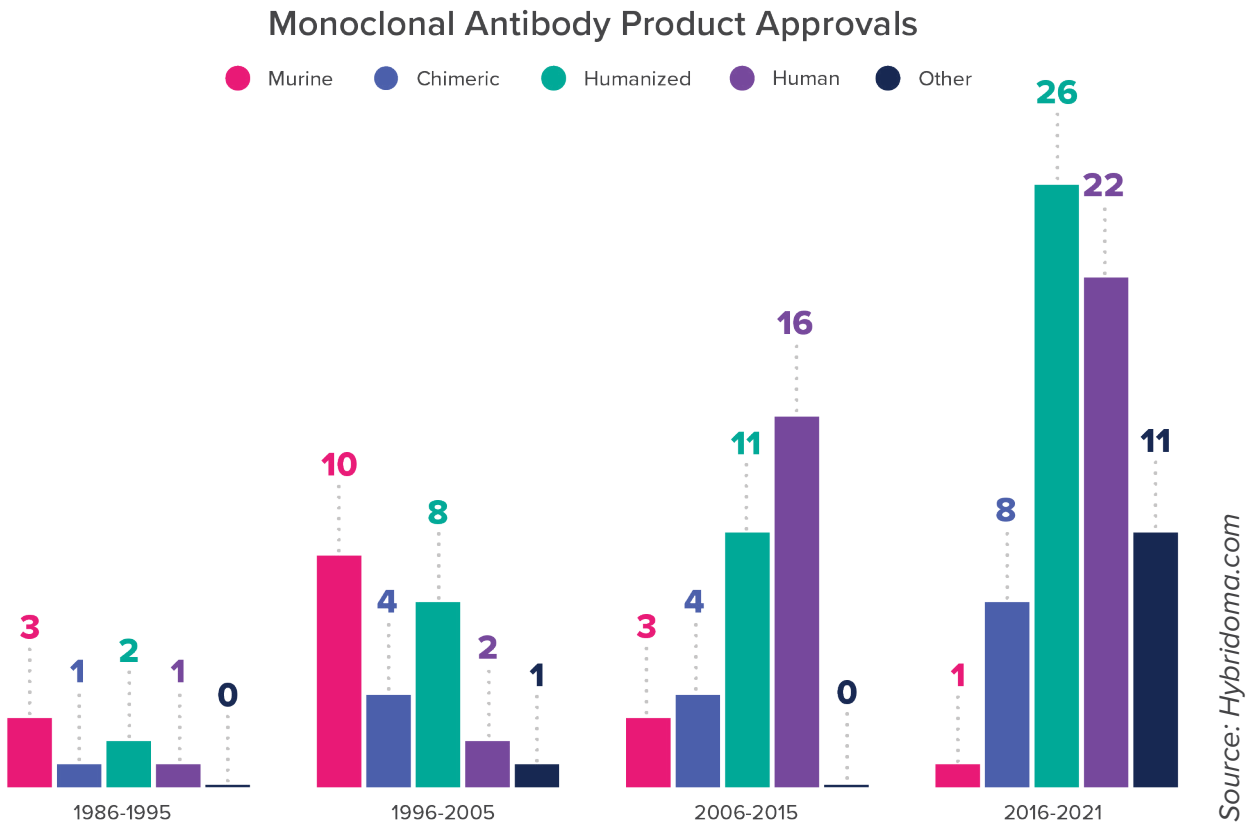
MONOCLONAL ANTIBODIES IN THE PIPELINE IN CONTRAST WITH RECENT PRODUCT APPROVALS

US and European regulatory agencies have now approved more than 130 antibody-based therapeutics since 1986. Monoclonal antibodies accounted for approximately 70% of total biopharmaceutical product sales in 2019—a 50% increase in just four years. Since about 2006, the trend in FDA approvals leans heavily toward humanized and fully human mAbs, which possess significant advantages over murine antibodies, including lower immunogenicity and longer half-life in vivo (Figure 5.8). Humanized mAbs represent the largest percentage of approved mAb products in the last five to six years, with fully human mAbs placing second on the list.

Before this became a well-established trend (between 1986-2005), murine antibodies were the most common class of mAb drug approvals. However, post-2005, murine mAb approvals rapidly dwindled against the rising interest in humanized and fully human antibodies.

FIGURE 5.8

Reference: Approved Monoclonal Antibody Therapeutics, Hybridoma.com.

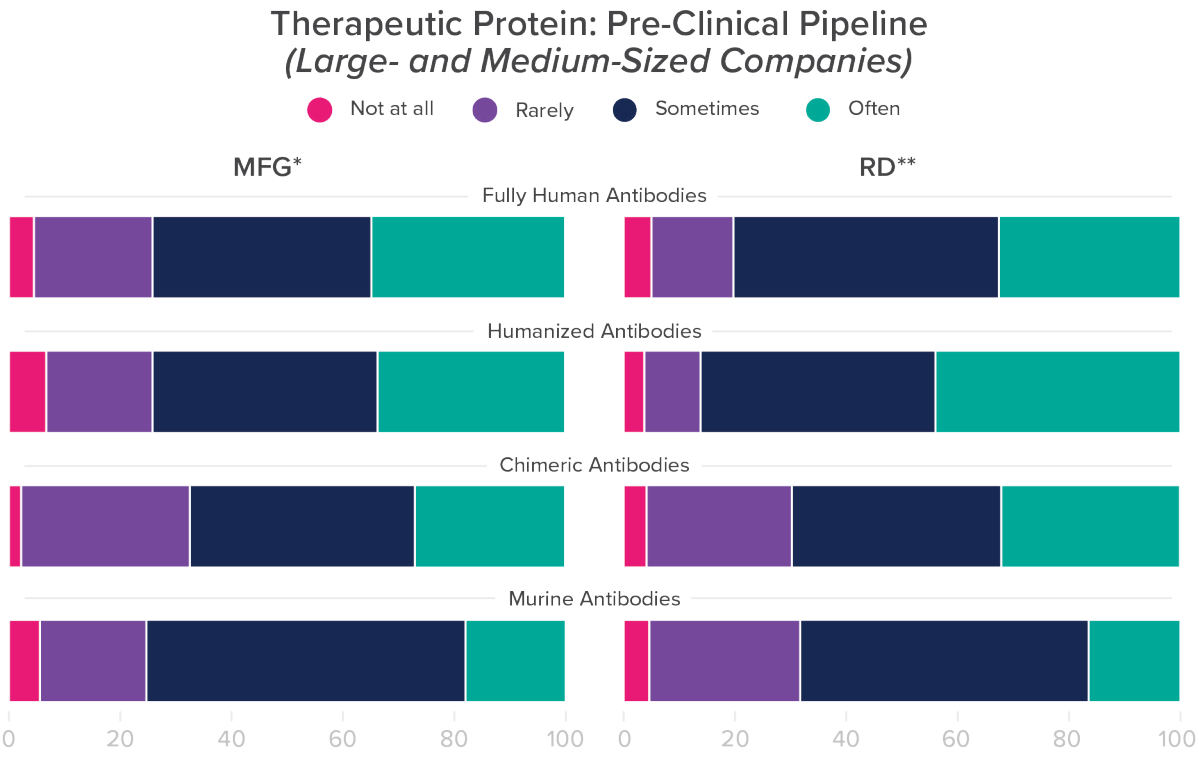


Source: Hybridoma.com

An interesting observation derived from our respondent data is the significant, ongoing research regarding murine antibodies (Figure 5.9). It appears that murine antibodies are still being evaluated as product candidates, although murine antibody product approvals have been virtually nonexistent since 2005. Conversely, the data indicates a prevalence in development pipelines of both fully human and humanized antibodies that are more congruent with their relative rates of drug approval.

FIGURE 5.9

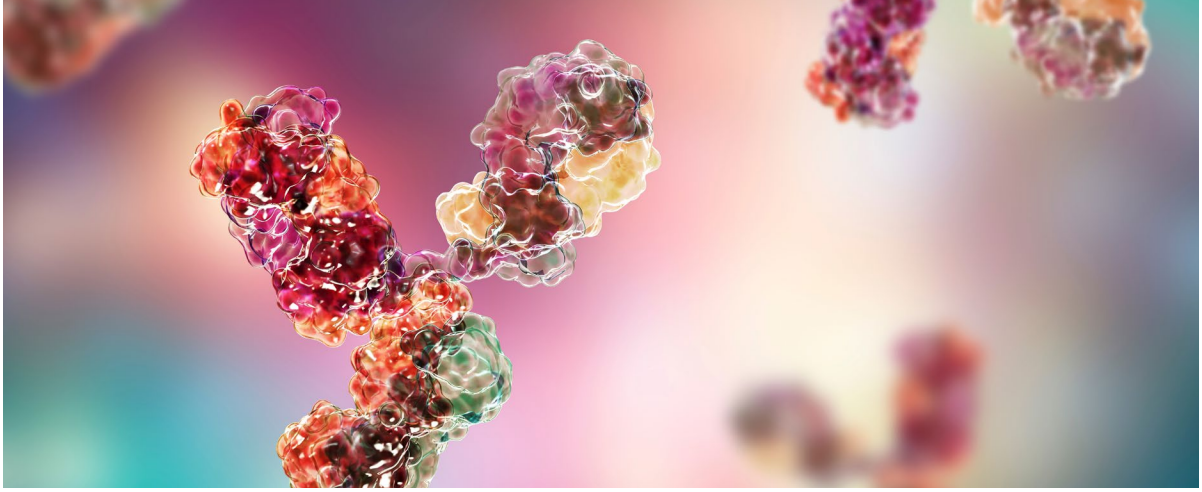
How often are the following monoclonal antibodies in your organization's pre-clinical development pipeline? (Multiple choice)



**Roles of process/product development, clinical manufacturing, engineering/facilities, capital projects, commercial manufacturing*
***Roles of clinical research, discovery and research, pre-clinical development, and translational R&D*

Source: CRB

Although we expect development of murine mAbs to recede in the future, as the approvals trend suggests, the indication of a significant murine mAb development presence paints a slightly different picture. While clearly less prevalent in development pipelines than humanized or fully human antibodies, murine antibody development may retain influence for several reasons—perhaps companies have traditionally maintained murine mAb platforms that continue to



prove useful in screening and discovery applications, or perhaps companies don't see an immediate need to abandon murine mAbs altogether. Whatever the reason, murine mAb development doesn't seem to be going away soon according to our survey respondents, who are in fact, mostly from the R&D space. However, based on mAb product approval trends, it is likely that the relevance of murine antibody development will continue to reside strictly in pre-clinical pipelines, with low probability of consideration as potential drug product candidates.

On a separate note, it's clear there has been an uptick in the "Other" category of the mAb approvals chart (Figure 5.8) during the last five to six years. This includes four rat-derived mAbs and seven primate-derived mAbs approved since 2016. Three of the primate-derived monoclonals were approved to treat SARS-CoV-2. For example, Sotrovimab was approved in 2021 to target the SARS-CoV-2 spike protein and clinical data suggest that the efficacy of this molecule is variant-independent. Considering this information, it is possible that drug makers on the leading edge of development are exploring mAb constructs derived from sources other than murine and/or human genetic material. Thus, future trends in mAb production may continue toward use of non-conventional genetic constructs.

Key Takeaway:

Murine antibodies are still relevant in development pipelines, despite therapeutic product approval trends since 2005 suggesting otherwise.

From antibody-based drugs to blood factors, growth factors, enzymes, and hormones, therapeutic proteins have saved countless lives over the last century and will continue to save many more as the industry acclimatizes to rapidly changing technologies, trends, and perceptions.

To stay ahead of the curve, manufacturers must take stock of these shifting tectonic plates and see what works to optimize their processes, whether it's single-use technologies, closed processes, continuous manufacturing, online real-time measurements, or even murine antibodies. The insights coming out of discovery and research will undoubtedly help manufacturers overcome challenges in manufacturing, and provide a strategic vision and an extra pair of legs to keep up with the ongoing breakneck speed of innovation. Whatever path we take in the development journey, our collective destination is at the hands of patients—bringing them safe, effective, affordable therapies in a timely fashion must be what shapes our choices.

Chasing tech in parenteral drug production:

Drug product manufacturers are leveraging new technologies, returning to blockbusters

By: Christa Myers

Section 6

As we emerge from the shadow of COVID-19 (while still planning for production of new vaccine formulations), significant changes to parenteral drug product manufacturing are also emerging. The warp-speed race that we saw two years ago in rushing drugs to market has segued to a steady pace, as developers and investors alike are taking stock of the advances, making adjustments, looking for onshoring opportunities, and thinking more strategically about the future of manufacturing.

Our *Horizons* survey data has shed light on several areas that showcase the current industry landscape, including the development of blockbuster drugs, persisting use of small batch sizes, and increasing complexity of drugs. The data highlights how the industry is marching forward with new technologies like automation and finding ways to save production costs.

As a large percentage of our respondents are from the research, discovery, and early development spaces, the observations we note in the following article provide unique insight into strategies stemming from R&D labs that look to the future and will undoubtedly influence, or perhaps even change the tide for commercial manufacturing in the years to come.

ARE BLOCKBUSTER DRUGS MAKING A COMEBACK?

What does *Top Gun: Maverick* have in common with today's drug production landscape?

Producers risked $170 million to make the movie. Within its first month on the big screen, it grossed $1 billion. A safe bet on a massive blockbuster—there's the common ground. In the last two decades, the life science industry has been edging away

from blockbusters and planning for “mini-busters” and personalized medicine. In parenteral drug product manufacturing, a blockbuster, a “mini-buster,” and personalized medicine are all on different types of machines and in facilities with different technical approaches.

Blockbuster drugs are a potentially lucrative option for life science companies, but they are also a challenge and a risk. If a drug fails in clinical trials because of an unforeseen side effect, inadequate levels of efficacy, being seconded by another product, or if its patent expires before its manufacturer has recouped its investment—if no one’s buying the movie tickets—it could be catastrophic for the parent company. Years of research and investment could be lost, seemingly overnight.

Many in the life science industry target smaller patient populations or rare disease markets. As the pandemic wreaked havoc and upended life as we knew it, the tables turned quite fast in drug development and money came flowing into never-before-approved ventures, such as mRNA vaccines and other mRNA products. The approval of the mRNA vaccines opened up the runway for many products through a manufacturing modality that was in the mere research stage just months before.

This “pandemic effect” may be why we’re seeing a renewed interest in blockbuster drugs in our survey data. Over half of the respondents have said that the primary target market for their company’s product pipeline is this blockbuster market around large patient populations (Figure 6.1). At the beginning of the pandemic, many research and development groups were already planning for therapies around the long-term effects of the virus. A great deal of research is going into cardiovascular and pulmonary therapies in order to support these after effects and patients experiencing “Long COVID.”

>50%

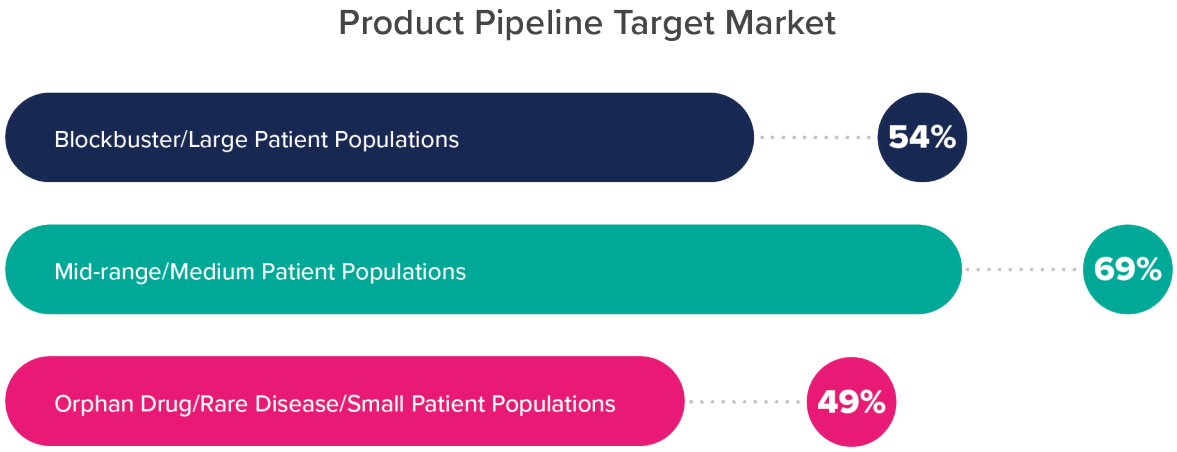
of respondents said large patient populations are the primary target market for their product pipeline

Research into COVID-19 vaccine production in particular, and other mRNA vaccines and therapeutics in general, may have triggered a shift that could change the profile of this industry over the next five to 10 years. For example, the number of drug product doses from an mRNA drug substance is much higher than for other biotherapeutic products, compared liter for liter. This could continue to push high-speed fill lines for large population products, even if the drug substance manufacturing facilities are small.

A wave of mRNA is not the only thing that is pushing high population products. In fact, at CRB, we have noticed somewhat of a resurgence in facility design proposals that include 20,000 L monoclonal antibody bioreactors and “six-pack” facilities (encompassing six very large bioreactors) for large-scale production. Depending on how companies view their business plan, this could push the industry into even higher scale and higher speed filling lines.

FIGURE 6.1

What is your company site's product pipeline's target market? (Yes/No)



Source: CRB

Considering that two-thirds of our respondents are from R&D and clinical research backgrounds, if the industry is truly pursuing blockbusters again, even at the R&D level, it will have a dramatic effect over the next decade on changing the size of drug production facilities and their level of flexibility. As such, the industry must remain flexible and prepared to accommodate both small batch (e.g., cell/gene therapy and clinical supply) and large-scale production (e.g., therapeutic proteins, mRNA, and plasma-derived therapeutics), because we will see an equivalent thrust in parenteral drug product manufacturing for all in the future.

Key Takeaway:

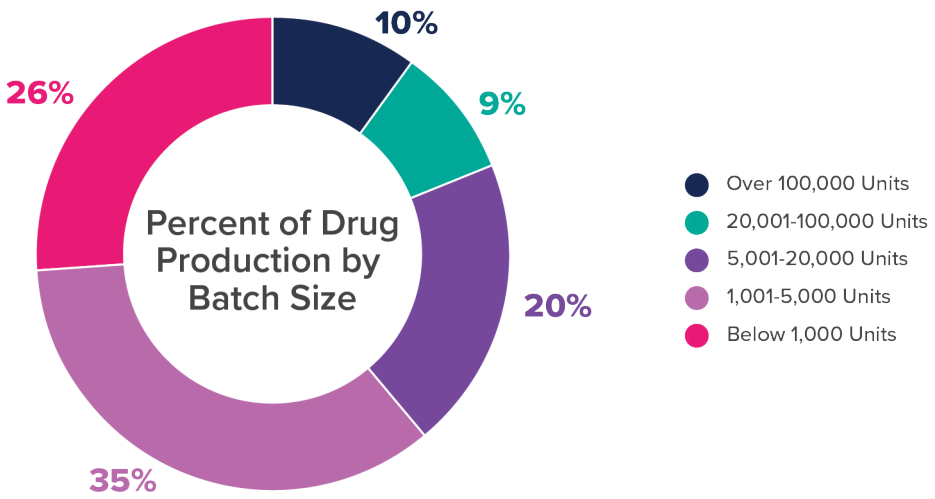
The future looks bright for drug production across all scales of patient populations: blockbuster, mid-range, and small patient populations.

BIGGER IS NOT ALWAYS BETTER: SMALL BATCH SIZES STILL DOMINATE

Our survey data indicates that small batch sizes remain more common across the board in parenteral drug product manufacturing. On average, respondents have estimated that roughly 60% of their production is dedicated to filling batches smaller than 5,000 units in size. Large companies dedicate a larger percentage of their drug production to batch sizes of >100,000 units compared to medium and small companies (Figure 6.2).

FIGURE 6.2

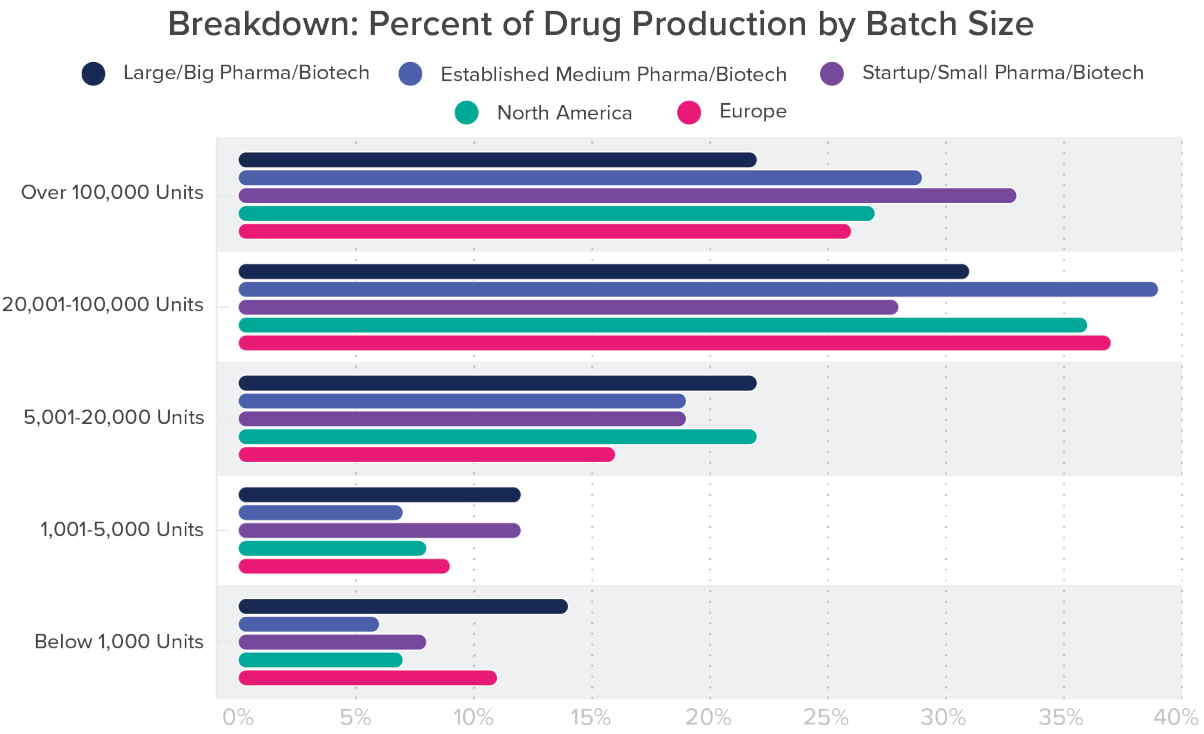
Estimate the percentage of your company's drug production that is dedicated to each of the given ranges of filling batch sizes. (Open entry)



Source: CRB

FIGURE 6.3

Estimate the percentage of your company's drug production that is dedicated to each of the given ranges of filling batch sizes. (Open entry)



Source: CRB

Since many of our respondents were from the research and development sides of their organizations, these batch sizes are not surprising. In clinical research, it is not unusual to see small batch sizes to support Pre-clinical, Phase I (less than 100 patients), or Phase II (less than 1,000 patients) Clinical trials. Even for Phase III Clinical trials (less than 3,000 patients), the number of units needed are low enough that only a handful of batches can be used to create the correct number of doses for the trial.

According to the U.S. Food and Drug Administration (FDA), 70% of medications will move from Phase I to Phase II. Approximately 33% will move from Phase II to III, and only 25-30% will make it to Phase IV (after approval). This translates to roughly 7% of medications reaching the finish line and getting approved. Many of the molecules that are being worked on in R&D today will never see a large patient population. The statistics change some each year, but the overall percentage of drug products that reach the patient is usually below 10% in the studies.

Small batch filling normally supports multiple products produced by the same or multiple R&D groups. Fill sizes larger than the aforementioned numbers are common due to testing of multiple dosage sizes when establishing a credible drug product plan. Fill line operations need to be tailored for the batch size and product, with a robust approach to quality, efficiency, and production costs—a "one-size-fits-all" approach won't work.

Another reason to rely on small batches is the cost of consumables. Vials, syringes, stoppers, caps, single-use fluid paths, etc., used for parenteral drug production are currently in high demand due to the ongoing manufacture of COVID-19 vaccines and therapeutics. Consequently, consumable costs have risen. A portion of these costs affects the overall drug price per dose. By limiting the batch size, companies can minimize inefficient usage of consumables and ensure a more cost-effective production per dose.

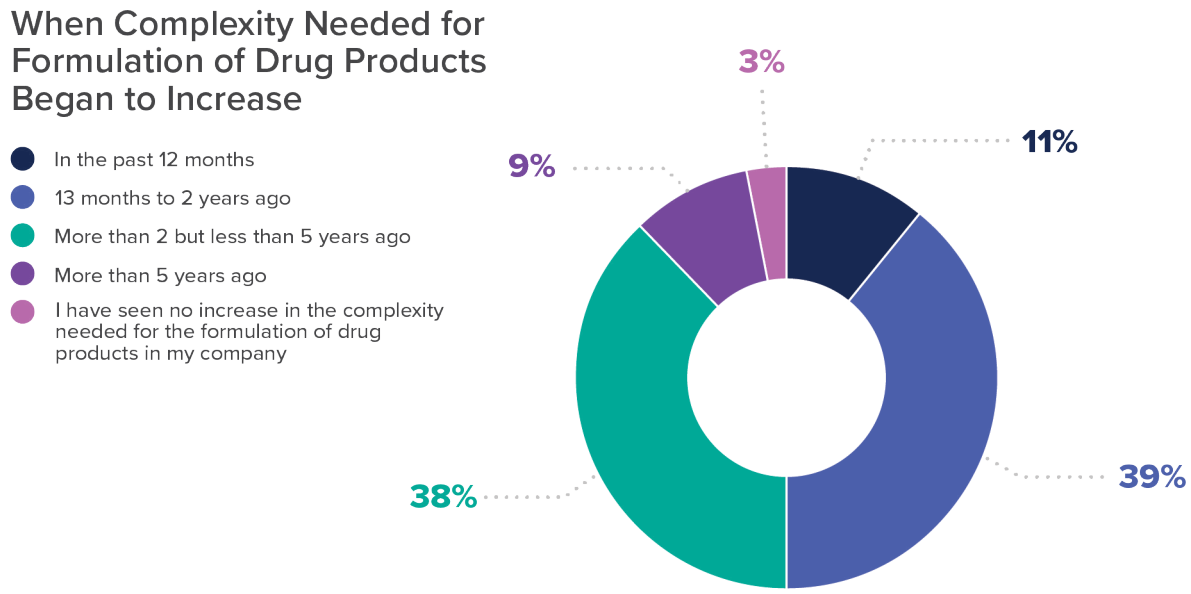
DRUG PRODUCT FORMULATION IS GETTING MORE COMPLEX

A vast majority (88%) of our respondents have noticed an increase in the complexity of drug product formulation within the last five years (Figure 6.4). Many new drug formulations utilize more complex drug delivery methodologies in order to deliver the drug product to a programmed location with lower dosages and lower systemic toxicities. Liposomal encapsulation, PEGylation, micellar encapsulation, and forms of nanoparticle formulations are not new within the drug product formulation world—but the lipid nanoparticle work involving the mRNA vaccine seemed to reawaken the story of more complex formulations.

One drug product form indicated as having significantly more growth in production than regular biological therapeutics, was antibody-drug conjugates (ADC). Many of our respondents (60%) have indicated being involved with ADC production (Figure 6.5).

FIGURE 6.4

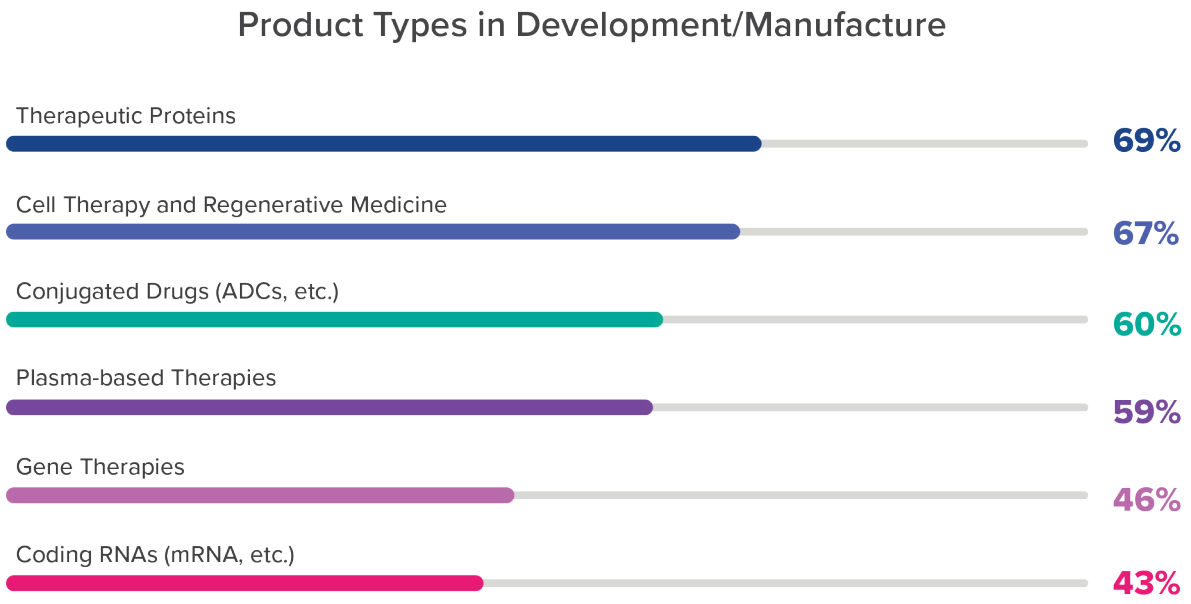
When did you begin to see an increase in the complexity needed for the formulation of drug products in your company? (Select one)



Source: CRB

FIGURE 6.5

What product types are your company's site currently developing and/or manufacturing? (Yes/No)



Source: CRB

Conjugation, linking, and purification steps associated with ADCs are more complex than other typical formulation operations. The conjugations, in particular, require delicate handling of the payload (due to compounds having a low occupational exposure limit or OEL) along with the linker and the mAb carrier. The conjugate is typically processed through purification steps in order to remove the non-conjugated/semi-conjugated materials from the solution and filled within a drug product fill line that must be designed for handling such potent OEL compounds. Many of these products are then lyophilized for stability.

There are a lot of design elements that must be considered when creating the infrastructure to support ADC production. The regulatory environment for the production of drug products that have low OELs is sensitive to the fact that there should be significant separation (physical and/or temporal) to prevent cross-contamination of products. There are also significant operational and environmental code issues to address with the facility, the equipment, and the waste material when designing a space to handle the production of ADC products well. This includes guidance from the FDA, the European Medicines Agency (EMA), CGMP officials, and also the Occupational Safety and Health Administration (OSHA), and National Institute for Occupational Safety and Health (NIOSH). The environment, the public, and the operator must all be considered, as well as the patient.

With the growth of the ADC market, companies should pay close attention to their formulation and compounding suites in order to adequately address the risks of contamination, cross-contamination, and operator exposure. The International Society for Pharmaceutical Engineering (ISPE) guidelines for handling low OEL (highly potent or highly hazardous) products, which CRB has been heavily involved in creating, may help with this aspect. For the ADC process, the right equipment and the right approach has to be measured against the actual risk of exposure and risk of cross-contamination at each step. For instance, a lyophilized powder presents a much higher risk of exposure, when spilled, than a liquid product. Different elements of an ADC process must be carefully considered when choosing the optimal engineered solution to protect product from cross-contamination and to protect operators from exposure.

NEW TECHNOLOGIES AND AUTOMATION TO MEET CURRENT MARKET PRESSURES

The widespread uptake of robotics and online monitoring at the lab bench/pre-clinical stage was a surprise in our data. More than 80% of our survey respondents want to implement online monitoring in the next five years; three-quarters also want to increase the use of robotics (Figure 6.6). This interest in new technologies at the clinical level is a massive jump from where things were a few years ago. Just two to five years earlier, clinical operations were barely dipping their toes into high-tech, automated workflows. Much of this change is a result of the lack of staffing in our workforce. Aseptic operators are some

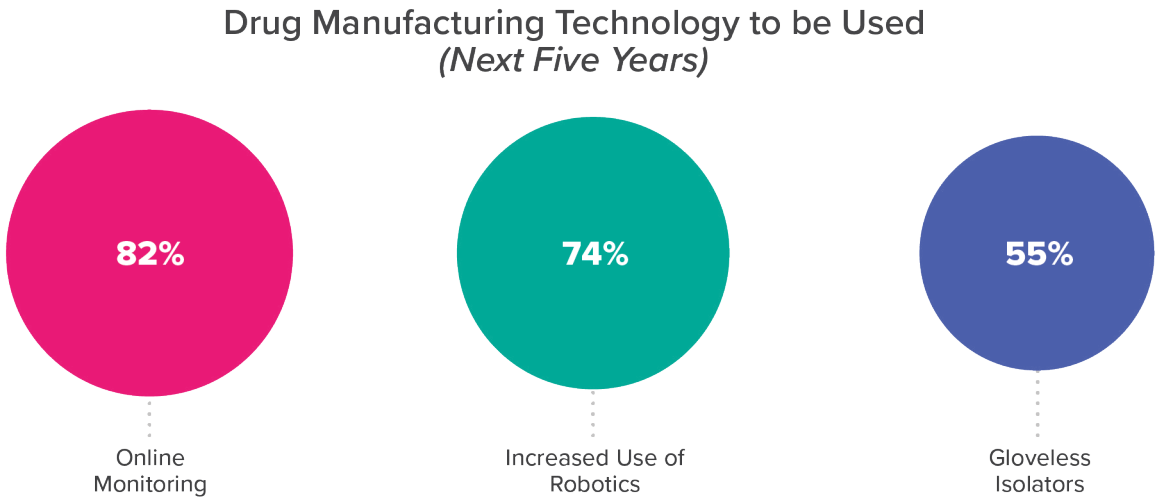
>80%

of respondents want to implement online monitoring in the next five years

of the most highly trained and sought-after staff in the industry. Any element that allows an operator to focus on a more critical aspect of the work is an advantage to the overall quality and quantity of product generated.

FIGURE 6.6

Is your company planning on using the following types of new technology for drug product manufacturing in the next five years? (Yes/No)



Source: CRB

In a tidal wave of change, R&D and clinical production operations now appear to be considering the implementation of online monitoring, gloveless isolators, and robotics. This change may be arising from the changes in commercialization, in order to ease technology transfer from clinical operations. Here are some of the pressures that are driving this trend:

Pressure to supplement CMO work with internal resources in order to win the "first-to-clinic" race and enable sufficient technology transfer

The life science industry is highly reliant on CMOs in the marketplace from clinical through commercial manufacturing. This strain on CMOs can be seen in the long lead times experienced at present by many of them. As a way to get around these production delays, and essentially take their future into their own hands, more and more operations companies are moving towards in-house manufacturing of parenteral drug products—62% of our respondents say their companies own in-house drug product manufacturing capabilities and 78% own in-house R&D capabilities.

This is implemented at several different scale levels depending on the product and company.

Bringing manufacturing in-house means companies have to be prepared to take on a whole new set of challenges and be especially mindful of improving/maintaining quality and saving costs along the way. Parenteral drug product manufacturing is already heavily automated, but companies are now pursuing longer-ranging automation that can reduce costs, equipment downtime, and improve quality issues. For example, online/inline monitoring, real-time feedback, quality control designs, vision systems, and robotics have a larger capital cost, but can have a huge impact on cutting down operational costs, which, in turn, will benefit both the manufacturer's bottom line and, ultimately, the cost to patients.

Pressure to move more efficiently through clinical testing

In the life science industry, the speed to market is a major driving factor for drug production. In an R&D business unit, the speed to clinic is just as important to meet speed-to-market demands. The use of online/inline monitoring technology and robotics can help increase these speeds, to the clinic and to the market, by reducing quality issues and human errors. Online monitoring provides real-time feedback to the production machine so that changes can be made immediately, reducing the risk of failure within a batch time rather than after an entire batch is completed. If the batch is at risk due to an unexpected exposure, the risk can be mitigated by a more interactive operations team, supported by real-time feedback. The production team can make critical decisions based on this feedback, preventing time, money, and even a whole batch of product from being wasted. This reactivity scales differently for small batches, or for batches of product difficult to make. For products with very limited production, the loss of one entire batch could cause a drug shortage for that set of patients. Any advancement that enhances quality and reduces risks is welcome to those business units and to those patients. A key question during early project planning is whether the cost is worth the added ability. Once a facility is operational, the operations team spends countless hours to improve quality and throughput of the facility, often going for the higher value options that provide higher quality.

Pressure to improve quality/consistency of CGMP manufacturing

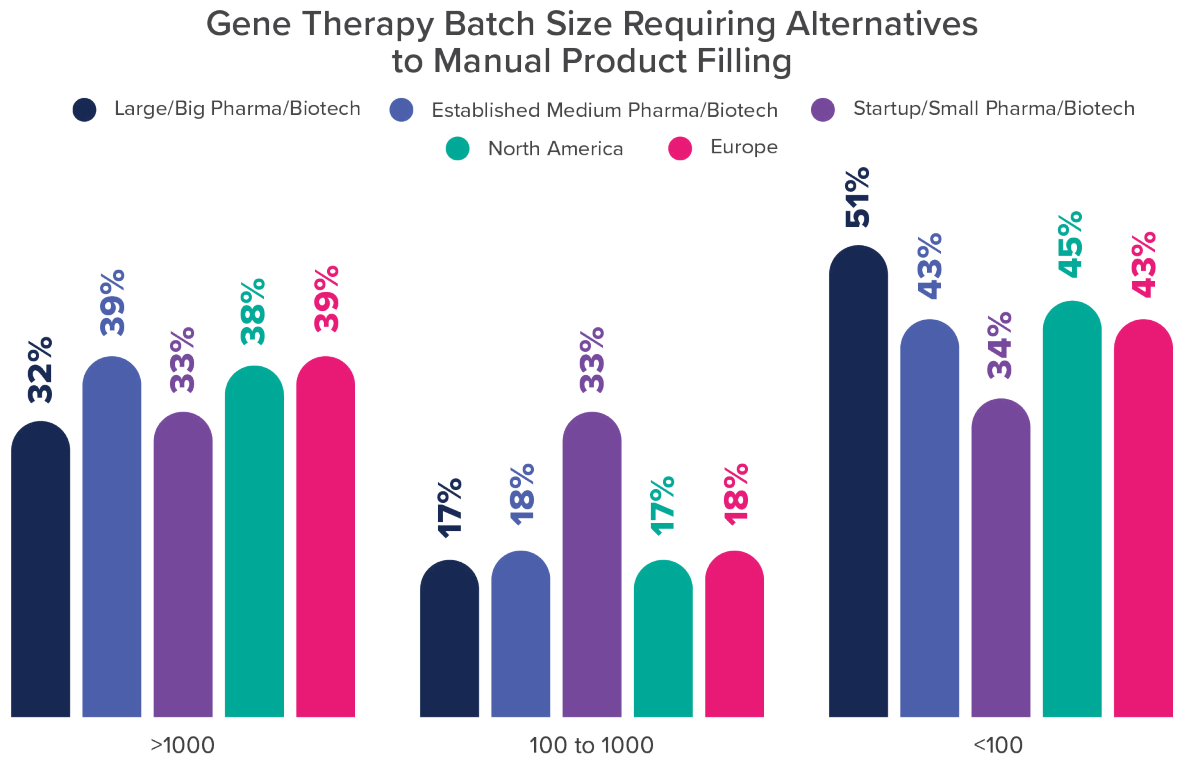
The use of robotics directly impacts product quality and consistency. Automation answers the problem of batch-to-batch variability to a large degree, as automated tools provide higher consistency in production and reduce the need for manual intervention. In a production suite where labor is at a premium, but also one of the greatest risks to product quality, robotics can help alleviate labor costs and eliminate human contamination—two of the greatest contributors to production issues.

Particularly in gene therapy drug product filling, our survey data indicates that companies tend to opt for automated alternatives to manual filling at batch sizes

below 100 units or above 1,000 units (Figure 6.7). Quality and safety at the patient level is the main element that drives innovation and regulation for parenteral drug products. As companies experience risks, their plans change. Automation can come in many different flavors to increase quality and reduce operator error. In gene therapy parenteral drug product manufacturing, half steps are being made to provide a more consistent result at the smaller scale, without jumping all the way to robotics filling. There are many semi-automated platforms available to enhance and control the quality of the product. Once again, the right solution scaled to the product is incredibly important in order to affect both the quality and the production costs of the parenteral drug product.

FIGURE 6.7

When considering business needs, at what gene therapy batch size do you feel you need to research alternatives to manual drug product filling? (Open entry)



Source: CRB

Key Takeaway:

Clinical production operations are setting a new pace for speed to clinic with the adoption of robotics and online/inline monitoring.

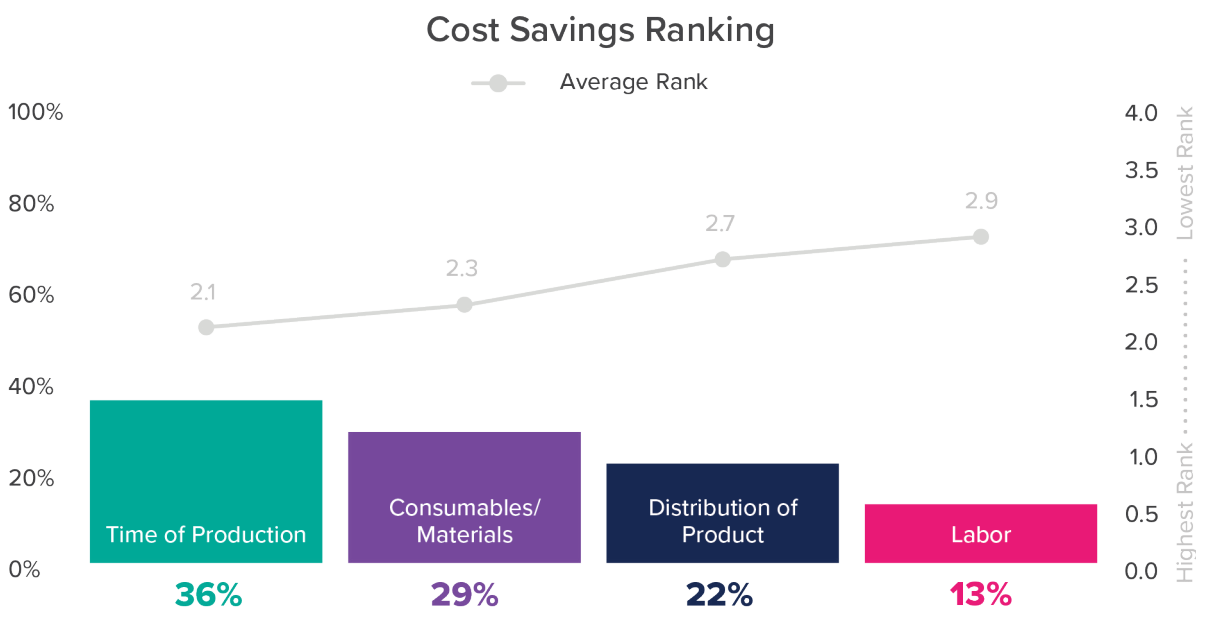
WHERE TO SAVE COSTS

A large percentage of our respondents believe they can save costs more effectively by reducing the time spent on production and reducing consumables/materials costs (Figure 6.8). Parenteral drug product manufacturing, for most clinical operations, is a complex operation that involves a variety of products and batch sizes. The time associated with production can be interrupted by changeovers—the big question for companies looking to reduce costs by speeding up timelines is how to manage changeovers between products and batches in the fastest possible way.

This, again, brings us back to the implementation of technologies like robotics and online monitoring which could trim equipment downtime. Even a gain of two more hours of product filling per day can increase the production capacity of a facility. This has an effect on clinical timelines, but when it comes to commercial-scale production, the difference is dramatic and critically important.

FIGURE 6.8

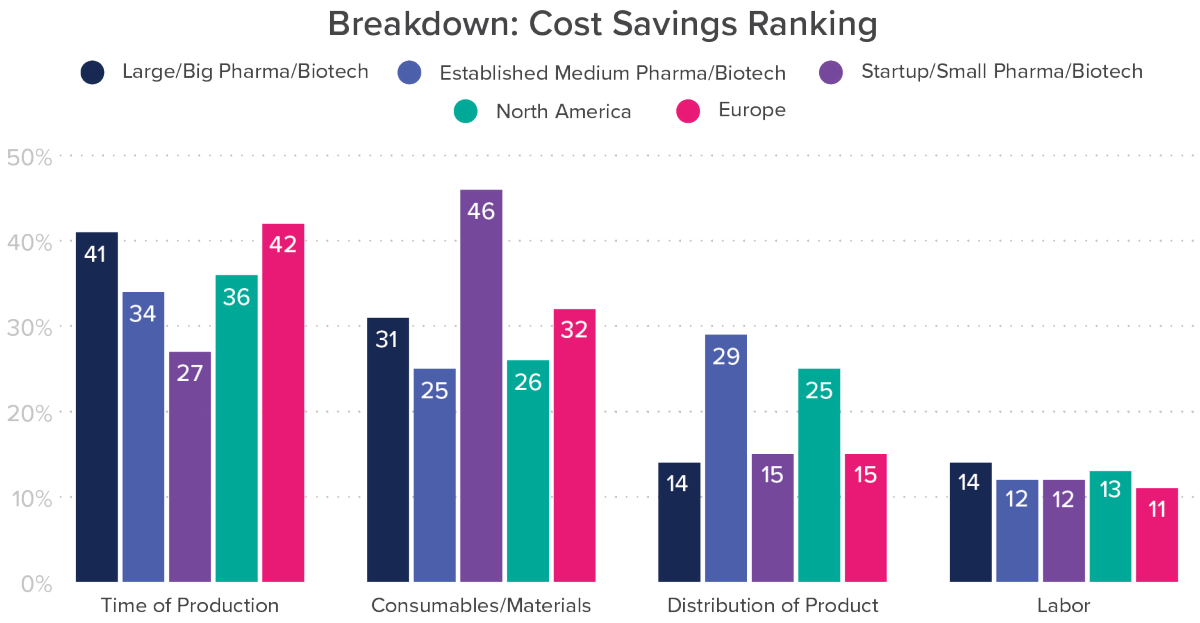
Rank the following in terms of where you believe your company could reduce drug product costs the most. (Rank order)



Source: CRB

FIGURE 6.9

Rank the following in terms of where you believe your company could reduce drug product costs the most. (Rank order)



Source: CRB

In the current clinical market, ready-to-use and single-use consumables contribute significantly to materials costs. Ready-to-use vials became incredibly popular in the past 10 years, both for small batch production of personalized medicines (such as cell and gene therapies) and for batches of clinical production scale. Ready-to-use containers, stoppers, and caps reduce the need for large equipment, usage of utilities, installation and qualification costs, and manual labor. Any reduction in the labor force reduces the risks and overall costs within onsite production.

It is clear why companies would choose to spend on ready-to-use consumables —but the demand has far outweighed the supply due to the burden of COVID-19, causing lead times and the costs of these consumables to keep rising. In fact, ready-to-use consumables can be significantly more expensive than bulk components, per component, and lead times can stretch to a year and a half or more for some consumables. Against this backdrop, it's very reasonable that manufacturers would want to change their methods to cut costs with consumables. It should be noted that the situation changes drastically from clinical to the commercial level, where bulk components are more common. This area of cost savings is very specific to the clinical or small batch market, and companies should be careful not to misapply this scheme.

We feel the need, the need for speed

What makes our jobs so interesting and meaningful is protecting the pipeline and ensuring finished drug products make it through clinical trials to commercialization, as fast as possible. Top Gun's top pilot, Maverick, would agree with "this need for speed" in bringing drug products to market.

As mentioned earlier, of all drug products that are developed in the pre-clinical phase, only 7% make it to the commercial phase. This number gives us some perspective on why an approach focused on high-quality, reproducibility, better technologies, and minimal errors is crucial for advancing the drug product field, especially for addressing challenges with complex formulations and varied business needs.

Drugs fail frequently for all sorts of reasons at various clinical stages. It's important to reduce failure risks due to quality or timing issues associated with production. A new miracle drug could miss its on-ramp to market and its one shot at reaching patients. That is an expensive loss for both the patient and the drug developer.

To position themselves as one of the rare success stories rather than those who tried but failed, drug companies need solutions and strategies that support a high-quality, scalable, and robust manufacturing approach from pre-clinical through commercialization. As such, technological innovations like online monitoring and robotics are salient elements to consider, not only for commercial but also for clinical production lines.

Scaling the digital mountain:

Cultural acceptance and rapid adoption of digital technologies is pushing Pharma 4.0™

By: Yvonne Duckworth

Section 7

When we canvassed industry experts for the last *Horizons: Life Sciences* report on the state of their efforts to bring digital technologies to biopharmaceutical manufacturing, we found an eagerness to embrace innovations in artificial intelligence, data analytics, and cloud computing. One year later, we see an evolution in the journey to implementing aspects of Pharma 4.0, such as smart end-user devices replacing paper records and engineers on the production line checking the status of a manufacturing batch on their phone or viewing predictive analytics in real-time on their iPad.

Yet ascending from one level of the Digital Plant Maturity Model (DPMM) to the next is a journey replete with challenges. At the top of the list are cost constraints, organizational reluctance, and a lack of labor with the skills necessary for a company to thrive in the digital age. While our findings about where companies identify themselves on that journey—and which level of digital maturity they'd like to achieve in the near future—are similar one year later, we did find encouraging signs that the industry is evolving as it shifts toward long-term innovation.

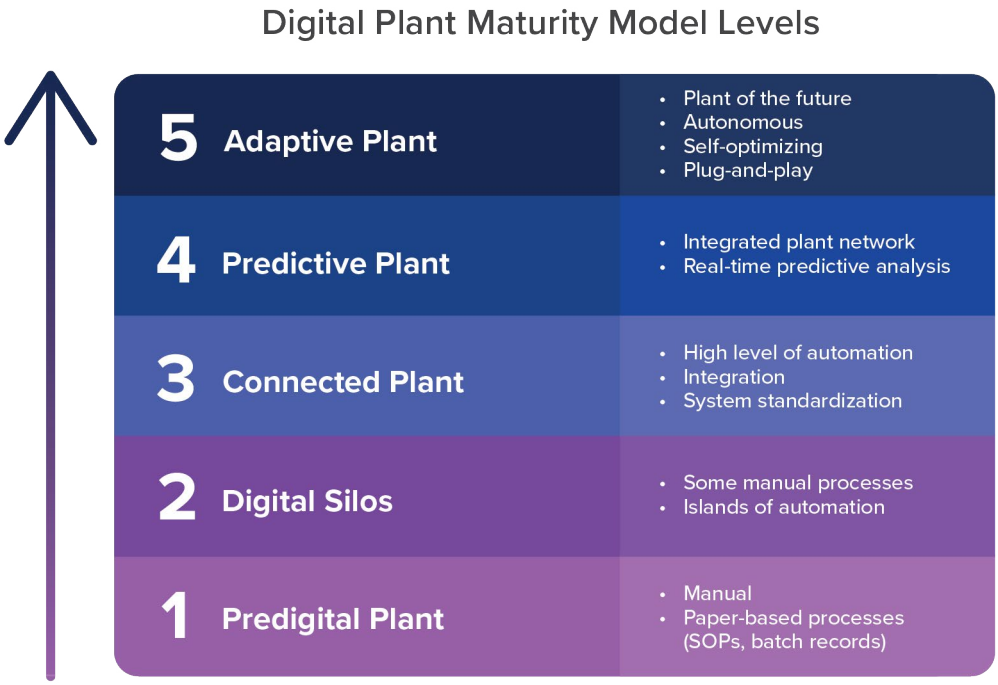
MOST COMPANIES ARE CONFIDENT THEY CAN REACH LEVEL 4 QUICKLY, AND EVENTUALLY, LEVEL 5

The DPMM provides a useful scale for assessing an existing facility's digital maturity (Figure 7.1). The peak of this scale—the Level 5 plug-and-play, adaptive/autonomous plant—may intimidate some companies at first glance, but we've seen a lot of progress towards digital maturity over the last year. The pandemic era introduced

new technologies and incentivized their adoption, helping companies grow more comfortable with the future of digital manufacturing. Our clients at CRB are typically at Level 3 and want to get to Level 4.

FIGURE 7.1

The levels of the Digital Plant Maturity Model as defined by the BioPhorum Group



Source: CRB

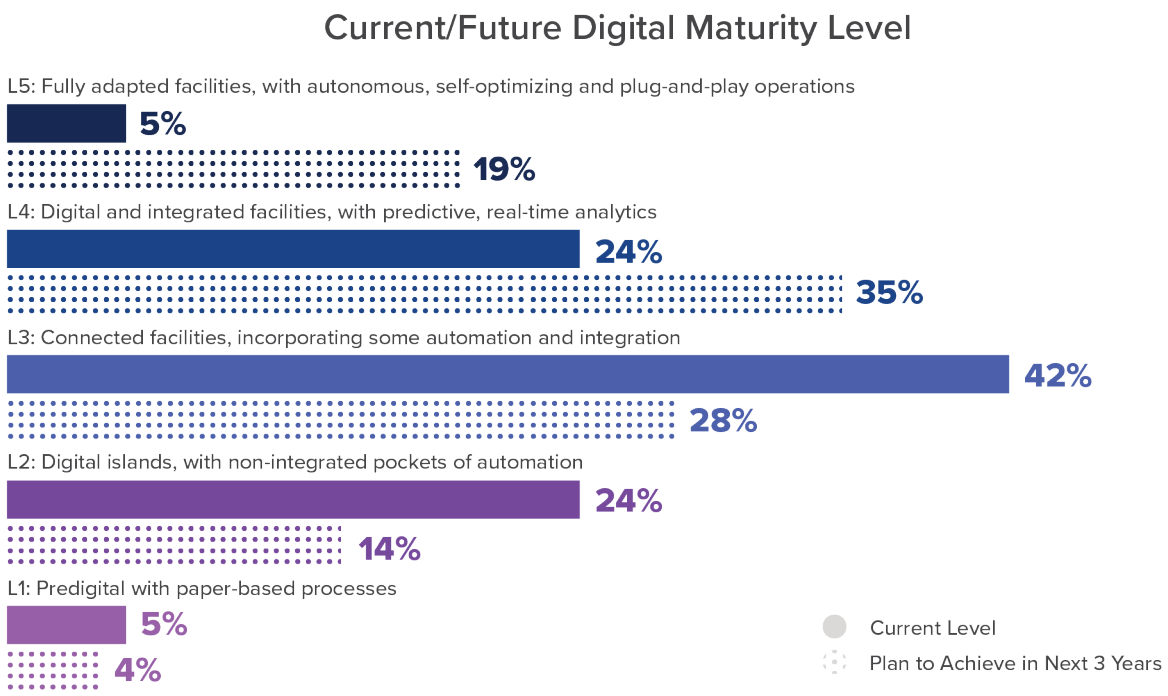
In keeping with our experience, almost two-thirds of survey respondents identify themselves at either Level 3 or 4 (Figure 7.2). While the differences between North American and European respondents were similar, survey respondents from large companies were most likely to say they have achieved Level 4.

It is worth noting that not all areas within a facility necessarily function at the same DPMM level. For example, a warehouse could be at Level 4, but the manufacturing spaces at Level 3. As respondents came from all functions, including clinical research (42%), R&D (24%), product/process development (13%), manufacturing (10%), and engineering (5%), it could be that some respondents were reporting what they experience in their role, not reflecting the facility as a whole.

FIGURE 7.2

Given the five levels of the Digital Plant Maturity Model, what level most accurately describes your company? (Select one)

Which level of the Digital Plant Maturity Model does your company plan to target to achieve in the next three years? (Select one)



Source: CRB

We found it surprising that 5% of respondents said their company is at Level 5 and that 19% intend to achieve that pinnacle in the next three years. In the past year, we have heard more companies talking about this, especially for certain areas within a facility, like a warehouse, where it's easier to manage the risks and measure the results of fully autonomous technologies.

Focusing on those aiming to get to Level 4, 63% estimate it will take them 19–36 months. This is in keeping with responses in 2021, when three-quarters estimated they'd reach the next DPMM level within two years.

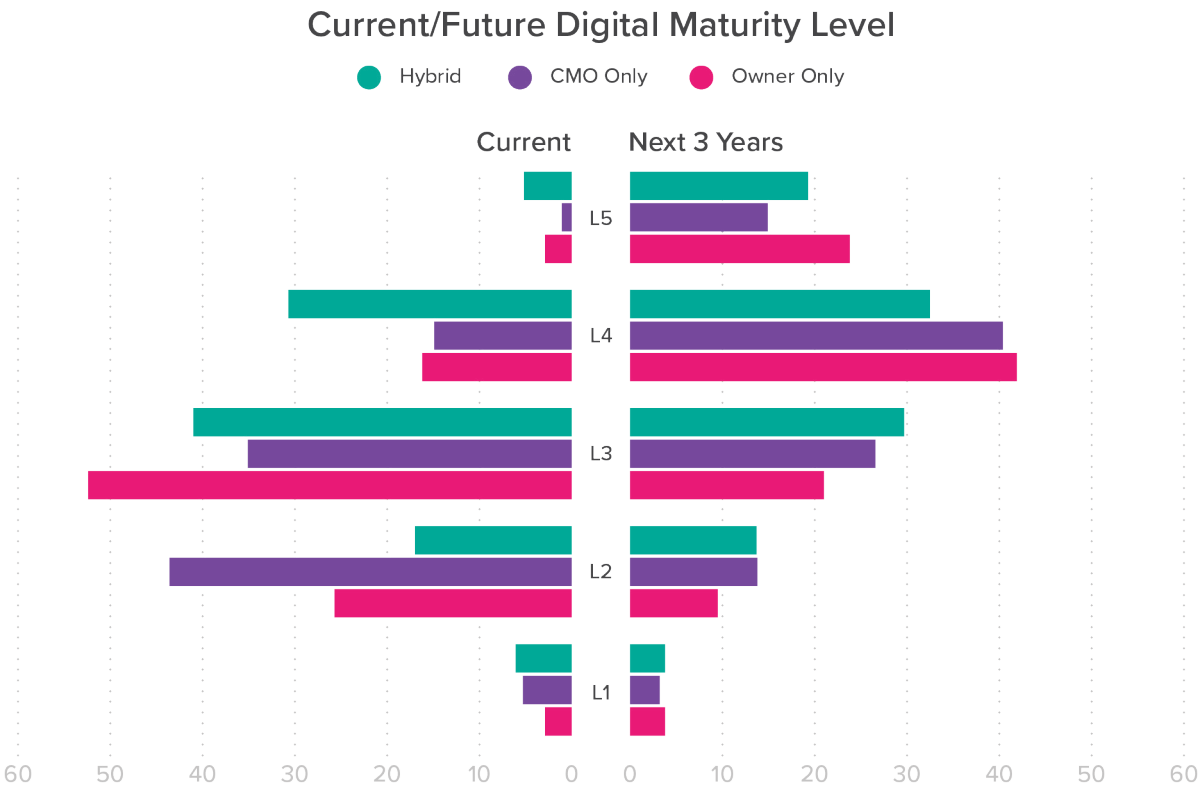
CMOs LAG BEHIND BUT ASPIRE TO CATCH UP

There was a significant difference in responses to current DPMM level between CMOs and owner-only organizations (Figure 7.3). The majority of those at CMOs identified their companies being at either Level 2 or 3 (77%) versus 69% of owner-only respondents choosing Level 3 or 4.

Given the cost of Pharma 4.0 upgrades, it may be that larger pharma companies are in a better position to absorb the costs of implementing these technologies.

FIGURE 7.3

Given the five levels of the Digital Plant Maturity Model, what level most accurately describes your company? (Select one)



Source: CRB

COST AND ORGANIZATIONAL RELUCTANCE ARE THE TOP BARRIERS TO IMPLEMENTATION

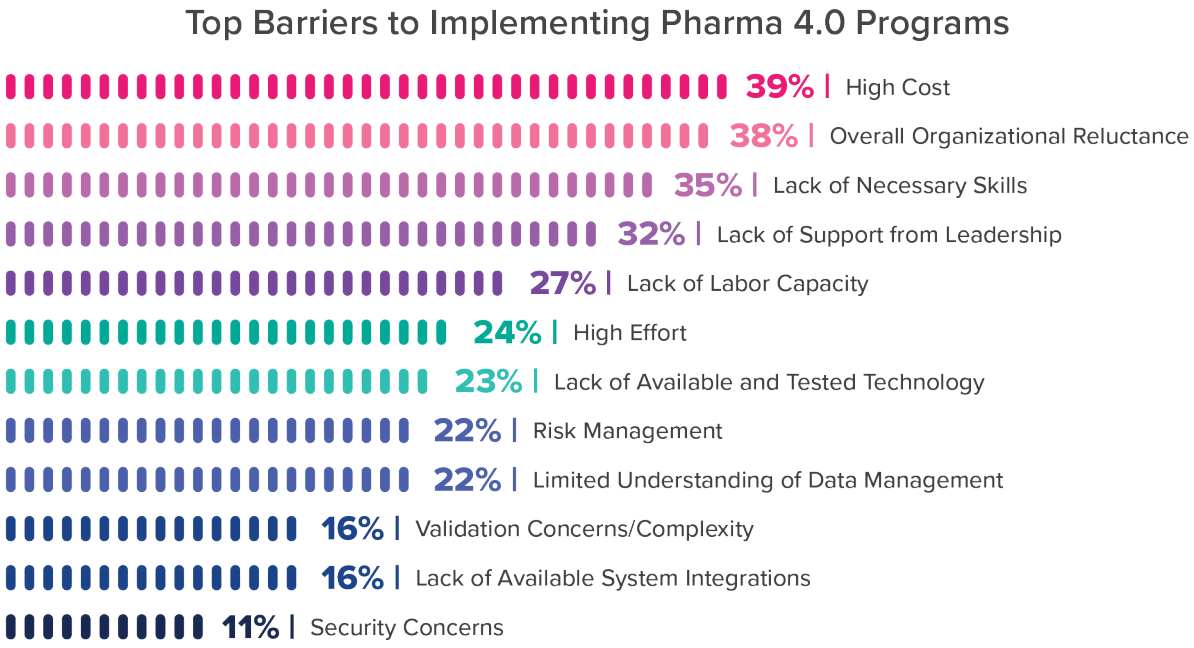
When asked to list the top barriers that their organizations face when implementing digital technologies, 39% of all respondents picked high cost (Figure 7.4). While upfront cost control will always be an important factor in planning, the long-term operational payoff of Pharma 4.0 is equally important. Far-seeing manufacturers who are laying the groundwork today for autonomous, digitalized systems in the future stand to reduce their downtime, batch loss, and incidents of human error, and they will enhance the safety and ergonomics of their workplaces. These benefits can net significant savings over time, more than offsetting that initial capital investment.

Interestingly, those with small companies/startups were much more likely to list cost as a barrier (63%) than medium or large pharma companies (35–37%). Startups are obviously focused on moving quickly while managing their burn rate—they simply want to get a viable product through clinical trials and into the market before they run out of money, which leaves little time to spare a thought for investing in future systems. But that line of thinking could be short-sighted. A startup that has developed its process to align with the requirements of a digitally mature commercial operation could differentiate itself from a pool of manually driven, paper-and-pencil competitors whose IP will need a lot of reverse engineering to fit into the portfolio of a digitally mature parent company.

Respondents also identified organizational reluctance and lack of support from leadership among the first four barriers. This highlights the role played by company culture in embracing digitalization, and it indicates a need to consider how digitalization will affect the work environment. Pharma 4.0 innovations do create new ways of working, and some workers may need time to adjust. Even activities that some may consider simple—like transitioning from writing process information on paper to entering it on a laptop, or typing in an electronic signature to having a biometric bracelet—can be intimidating for some, especially those with a long career in an industry that has seen accelerated change over the last few years.

FIGURE 7.4

What are the top three barriers for your organization to implement Pharma 4.0 programs? (Rank order)



Source: CRB

Security concerns were low on the list of reported challenges (11%), which is a heartening change from the last *Horizons* report that had security in third place. This is surprising, but could indicate that the industry is growing more comfortable accepting the security risk and is adding measures to protect its assets.

We've seen that more people are willing to store data in the cloud, which is a big change from even five years ago. Also, many companies, having recognized the overlap between information technology (IT) and operational technology (OT), have merged their IT and OT groups, with both teams reporting to the same people. This overlap no doubt helps alleviate some of the security problems.

THE CULTURE OF ORGANIZATIONS IS EVOLVING TO EMBRACE DIGITALIZATION—A CHANGE THAT STARTS IN THE C-SUITE

The good news is that, despite a sense among some of the respondents that reluctance within the organization and lack of support from leadership are holding them back, it is the C-suite that appears to be owning the process. When asked who was sponsoring their company's Pharma 4.0 initiatives, the Chief Technology Officer (CTO) and CEO topped the list (Figure 7.5).

Leadership needs to consider which innovations to introduce into an organization, as well as big-picture thinking to adjust company mindset to accommodate new ways of working.

The apparent contradiction between lack of support from leadership topping our respondents' list of barriers (Figure 7.4) and the apparent buy-in from the C-suite may be chalked up to the time and expense involved in making the transition from one DPMM level to the next. Let's not forget that even five years ago, most companies would not have had a Chief Information Officer or a Chief Data Officer. The creation of positions to lead these initiatives demonstrates the high level of visibility that Pharma 4.0 has in our industry; companies realize that propelling Pharma 4.0 initiatives forward requires introducing the right skillsets into the C-suite.

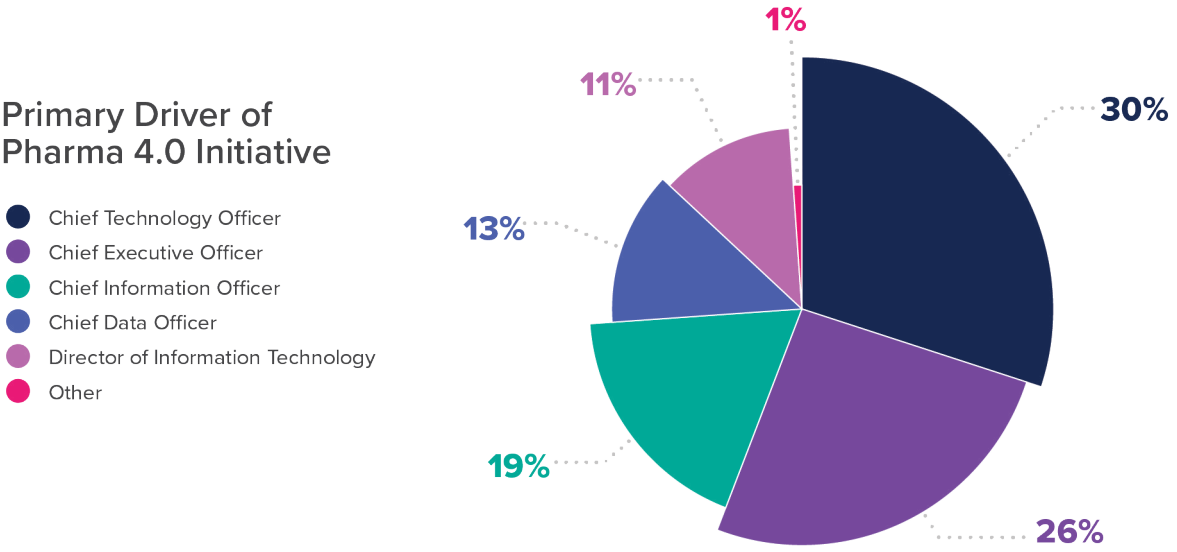
When asked who was sponsoring a Pharma 4.0 initiative, those from different types of organizations offered very divergent responses (Figure 7.6). For CMOs, this was predominantly the CEO (37%), for owners, it was the CTO. This aligns with what we're seeing in the industry, with large companies pursuing digitalization more aggressively than CMOs. CMOs do require a greater level of flexibility, which may make it difficult to integrate a one-size-fits-all digital solution.

Large companies

are more aggressively pursuing digitalization

FIGURE 7.5

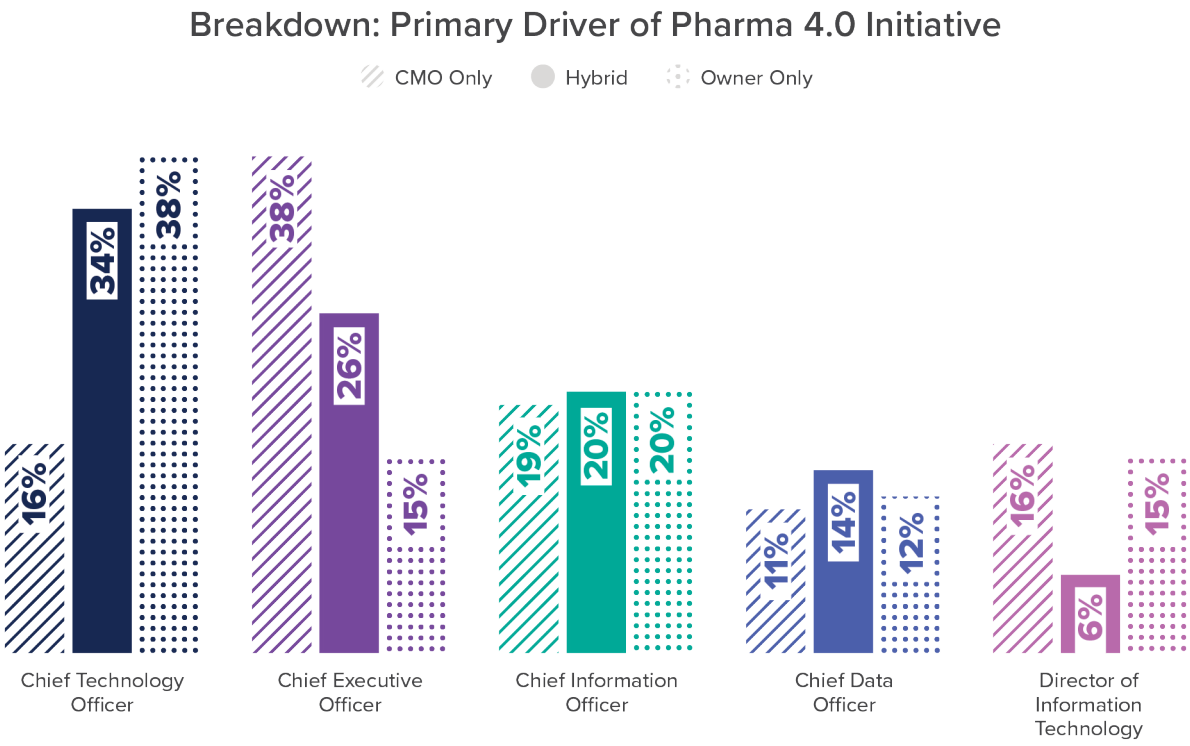
Who is driving, as a sponsor, your company's Pharma 4.0 initiative? (Select one)



Source: CRB

FIGURE 7.6

Who is driving, as a sponsor, your company's Pharma 4.0 initiative? (Select one)



Source: CRB

LACK OF SKILLS AND LABOR CONTINUE TO BE AN ISSUE

The technologies needed to get to Level 4 of the DPMM require specific skill sets, some of which may be new to the industry. For example, introducing a data analytics system means hiring data scientists or data analysts, both of which are a hot commodity in many industries.

This is one of the few instances when responses from those in North America differed from the Europeans. In the EU, a lack of necessary skills is perceived as a significant barrier (43%); in North America, that number falls to 31%. On the other hand, North American respondents are more likely to identify a lack of labor capacity as a challenge (39%) versus respondents from the EU (22%).

TODAY'S MANUFACTURERS ARE RAPIDLY ADOPTING DIGITAL TECHNOLOGIES

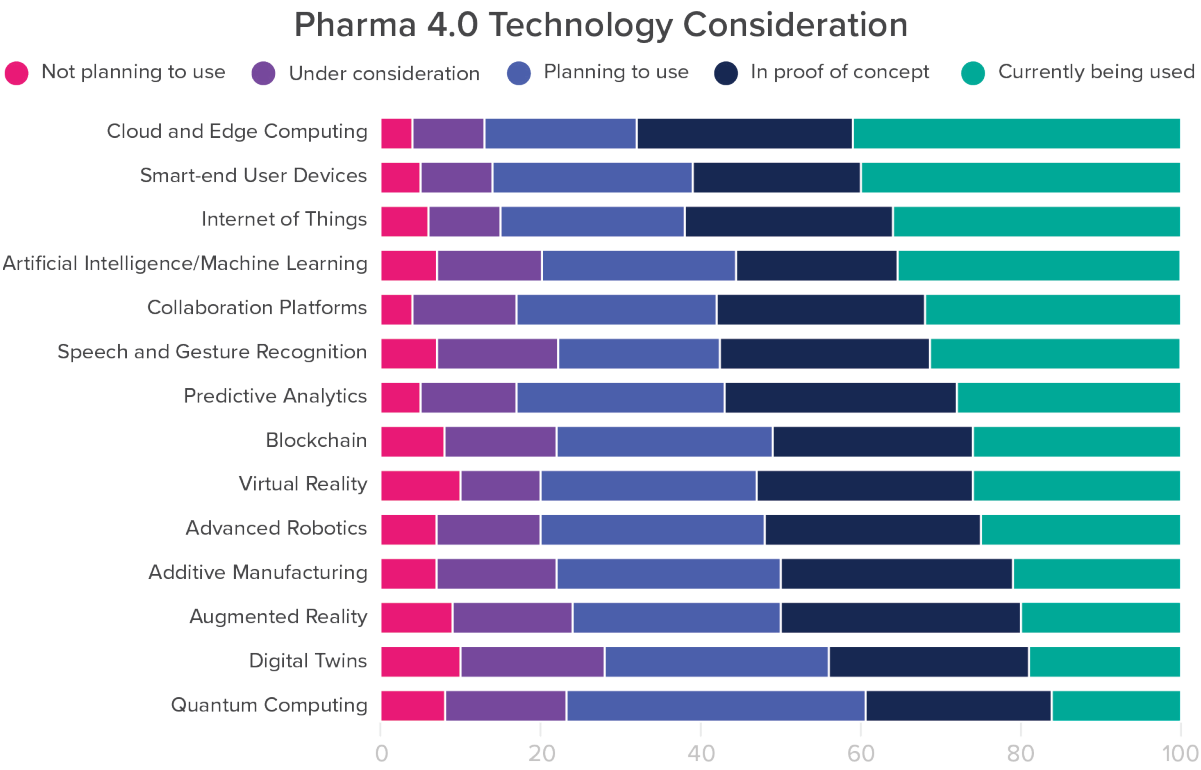
To achieve Level 4, companies need to embrace a number of technologies, chief among them: smart end-user devices, the Internet of Things (IoT), predictive analytics, AI, and machine learning. It is great to see that for these and most other Pharma 4.0 technologies listed in Figure 7.7, more than half of respondents say their companies are either using these or have them in the proof-of-concept stage. A few examples include:

- **Smart end-user devices:** This can be as simple as having a data historian on a user's phone or tablet. The digital delivery team at CRB uses a 360° camera to capture images of a manufacturing area. This allows users, for example, to touch a valve on the screen and retrieve the valve's specification sheet and user's manual. This can essentially provide a digital blueprint of a manufacturing area, along with the capability of accessing important data in a digital manner.
- **Advanced robotics:** We've seen many equipment vendors push forward with robotics, especially in filling and packaging areas where repetitive manual tasks have predominated. Robotics can increase efficiency, decrease human error, while improving safety and ergonomics.
- **Blockchain:** While more than half of respondents say blockchain is currently in use or in proof of concept, this is not our experience. While there is desire and a willingness to use blockchain, it is optimistic to think our industry is prepared to embrace it. Some large companies are experimenting with applications, and we look forward to seeing where this leads.
- **Digital twins:** These virtual representations of a facility use real-time data to help users understand how it works. CRB uses them for design verification and to track progress.

We are seeing more interest in Pharma 4.0 from labs. This is encouraging, because labs that start from a 'digitally native' position will find it much easier to adopt emerging technologies and adapt to an increasingly automated world, giving them a significant advantage in the climb towards digital maturity.

FIGURE 7.7

For each of the following Pharma 4.0 technologies, rate the degree to which your company is considering using it in the next five years. (Multiple choice)



Source: CRB

From the peak of digital mountain, the view is clear

Overall, the responses revealed continued interest in integrating more mature, sophisticated systems into the plant. They show the uptake of digitalization is trending in the right direction. The enthusiasm is there for companies to keep climbing that mountain.

Technological change is a journey, not a stopping place, and survey respondents appear to be saying that those aiming for the summit need to embrace Pharma 4.0, get their leadership involved, and keep putting one foot in front of the other.

A Case for Modular Design:

Life science innovators are turning to modularization for greater operational agility, adaptability, scalability, and resilience

By: JP Bornholdt & Daniel Fritsche

Section 8

You wouldn't know it to look at the line-ups for the latest model of the iPhone, but the technology under the glass only undergoes minute changes with each passing evolution. Aside from a small set of variants, each unit is identical, but yet can perform a virtually endless list of functions for its owner. With each iteration, Apple learns more about the end user's experience, and they apply that learning as streamlined improvements to the relevant components. The end user remains familiar with the layout and functionality, while the back-end technology improves with each generation.

That's modularization at work. It's an agile and adaptable design approach that builds resiliency into end products while laying the foundation for fast and cost-effective future scalability. And it's not just the domain of consumer tech giants. Increasingly, project owners in the life sciences are learning to embrace a modular approach as the key to enabling and accelerating their business plan across a global manufacturing landscape. In fact, 63% of our respondents identified the use of preconstructed speculation space to pursue lab/CGMP site expansion.

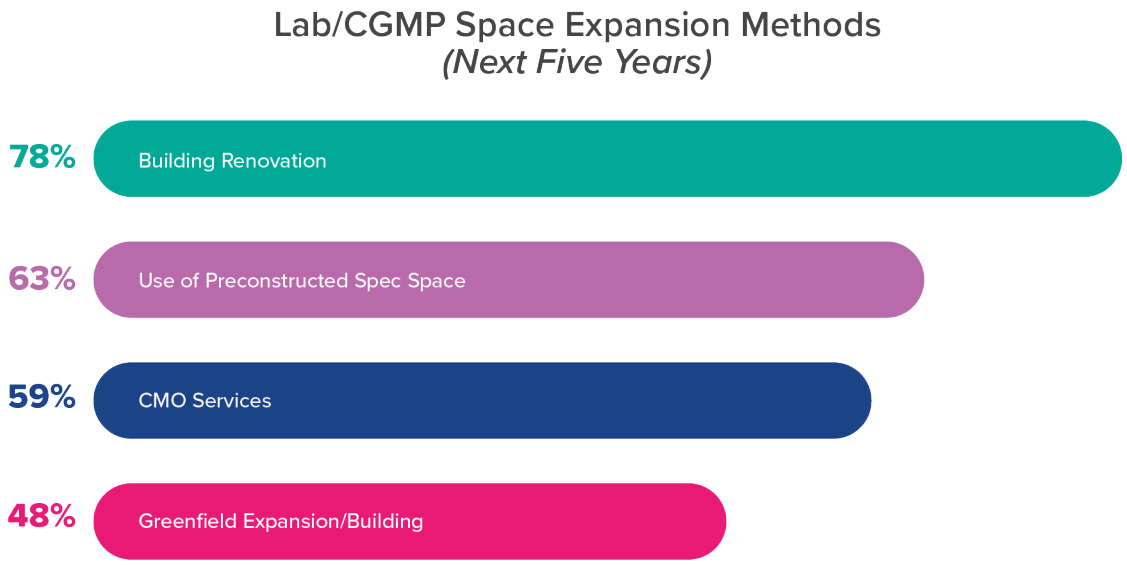
63%

of respondents identified the use of preconstructed speculation space to pursue lab/CGMP site expansion

Given that most of our nearly 500 *Horizons* survey respondents plan to expand over the next five years, with some even indicating intent to establish additional operations in other countries, this shift to modularization is underway just in time.

FIGURE 8.1

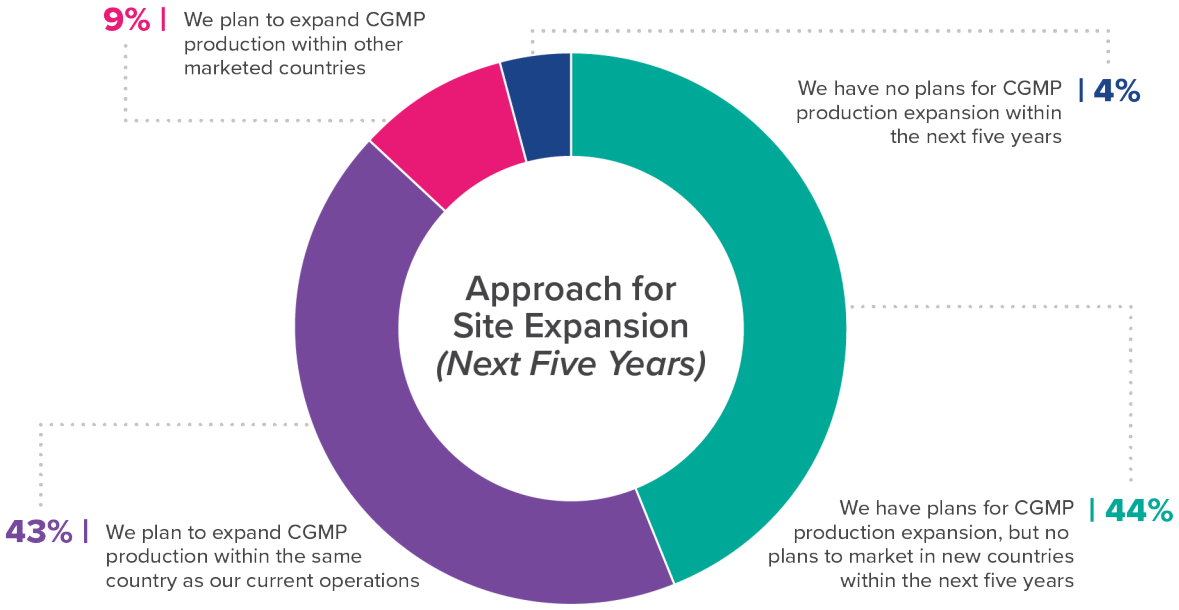
Within the next five years, is your company planning to pursue lab/CGMP space expansion using one of the following methods? (Yes/No)



Source: CRB

FIGURE 8.2

If your organization is marketing/intending to market products within a country other than the one you manufacture products within, what is your organization's approach for site expansion within the next five years? (Select one)



Source: CRB

Whether or not a multinational expansion is in your crosshairs in the short-term, moving beyond the limitations of bespoke design is advantageous. Companies who leverage agile and adaptable components, (work cell modules, standardized floor and wall panels, or speculative cleanrooms, for example) are better positioned to:

- Future-proof their facilities to accommodate a changing workforce, supply chain, and digitization landscape.
- Maximize operational improvements and efficiency across both CAPEX and OPEX planning.
- Rapidly scale up production and introduce new modalities as their business case demands it.

But how does modularization actually enable these benefits? What can those considering a shift away from "business as usual" design expect from a modular future—and what should they do today to get the most from this shift?

MODULARIZATION IMPROVES OPERATIONS

There's a pervasive myth in the life science industry that choosing a modular approach means giving up flexibility or control. In fact, when leveraged appropriately, modularization has the opposite effect: it increases the agility and adaptability of a project's design. That's because modularization decreases and defers the burden of making mission-critical design decisions, giving project teams the opportunity to learn, adapt, and scale rapidly.

Instead of locking into a detailed design from day one—which makes it costly and time-consuming to adapt when downstream change orders arrive—project teams with a modular approach start with a modest buildout that meets immediate business needs, and expand iteratively from there, integrating new equipment, technologies, utility hookups, and other operational improvements over time. This means the distance from concept to initial operation is much shorter than in a traditional "go big" design approach—and the opportunity to learn and adapt is much greater.

There's another benefit to modular design related to simplified decision-making: because the controlled and repeatable conditions of a factory make it simpler and faster to produce modular components compared to bespoke on-site construction, project teams can defer certain technical decisions until later in their delivery lifecycle without compromising their overall project schedule. This further expands the project team's ability to clarify business and process drivers and details, integrating "lessons learned" and iteratively optimizing their approach with each project phase. It's the agile Apple methodology, writ across a life science manufacturing network: release a product (an iPhone, or a CGMP cleanroom module), learn from its end users, make improvements, and expand incrementally with an updated, optimized iteration. If that isn't flexibility and control, what is?

CASE STUDY: A mRNA MANUFACTURER ADAPTS A MODULAR DESIGN FOR ACCELERATED DEPLOYMENT

A modular approach doesn't only decrease and defer the burden of upfront decision-making, though; it also simplifies that burden at the source by standardizing some or most of the design itself, while allowing room for unique adaptations and agile decision-making.

That's what recently attracted a multinational mRNA manufacturer to a modular approach. They were on the threshold of a critical manufacturing milestone that would massively expand in-house production to many new sites around the world. To prepare for that day, they needed to establish manufacturing facilities in markets where they hadn't operated before, and they needed it now. They leased a local shell building and worked with our team to identify a modular CGMP suite that fulfilled 80% of their criteria; that left them with just 20% of the suite's design to adapt when building new facilities in new geographic conditions—a much simpler, faster, and more agile decision-making process.

To further accelerate deployment and take advantage of the resilience and scalability of modular design, they divided their delivery milestones in phases:

Phase I – Two modular CGMP suites in the local building shell, utilized for clinical and process development.

Phase II – Scale-out two additional CGMP manufacturing suites at a remote location, with new modules adapted and optimized according to Phase I insights.

In addition to accelerating their commercial manufacturing expansion, this modular approach also positions our clients to strategically control their facility's operational costs through continuous, iterative operational improvements, and it prepares them to manage the facility's end-of-life costs more effectively; in the years to come, if their geographical needs change or other shifts impact their network strategy and business plan, they can relocate these modules around the globe as needed.

MODULARIZATION ENABLES CONSISTENCY

When it comes to manufacturing, 53% of our *Horizons* respondents with multi-site operations reported some challenges in adhering to standards and procedures across their CGMP sites. Larger companies reported the least challenges with regards to adherence compared to their smaller peers. While initially counterintuitive, given they likely have larger footprints to manage, larger companies might also be more likely to have the ability to employ teams devoted to standardization and expansion strategy compared to smaller companies and start-ups.

Thoughtfully planned phased expansion can help to mitigate risks by enabling consistent standard operations and operating procedures across a company's whole manufacturing network. This level of consistency enables a streamlined training approach, which sets operators up for success. Instead of dealing with one-off scenarios, operators face repeatable and predictable scenarios across spaces (and even facilities) that allow them to do their job more effectively in more locations.

This offers flexibility to both the operator and the owner, as operators can be more easily onboarded and relocated when the need arises for the company or the individual. Moving into a facility with near-identical components affords a level of familiarity that is extremely valuable in a landscape where human error can result in the delay or loss of batches of life-saving therapies.

The result is a more productive workforce, reduced risk for the owner, and—ultimately—improved outcomes that will benefit the patient whose health depends on consistent, high-quality products.

MODULARIZATION STREAMLINES REGULATORY COMPLIANCE

Of the potential challenges that can slow a new facility's launch, the regulatory approval phase looms large, delaying a facility's occupancy, production schedule, and profitability.

This is where ensuring the compliance of one small but exemplary buildout can prove to be an effective speed-to-market strategy. Companies can learn from early deployment phases and apply those lessons as they scale through modular deployment, rather than combing through multiple variants at multiple sites. In this scenario, each successive iteration of modular delivery can provide regulatory feedback that may be directly applied to future regulatory applications, accelerating each successive regulatory approval, and also streamlining operations. Regulatory compliance is just one example of how the standardization granted by modular design can improve operations across a network of facilities.

Establishing a regulatory strategy with modularization as its key component is also hugely beneficial when it comes to multinational expansion efforts. Reconsidering and redesigning facilities in multiple countries is burdensome for most companies, and leaves room for inconsistencies between sites. That's where modularization can play a key role: by certifying each module within a global manufacturing network to satisfy the highest and most universally accepted standards, owners can reduce the headache of customizing each facility according to local standard operating procedures and practices.

MODULARIZATION FACILITATES DIGITAL MATURITY

Our *Horizons* survey suggests that the life science industry is increasingly trending toward integrating technology into its operations. A sizable portion of our respondents (42%) described their facilities as connected, incorporating some automation and integration. Within the next three years, 35% reported plans to move to digital and integrated facilities, with predictive, real-time analytics (Figure 7.2, page 79). The implementation of standardized, modular design elements sets companies up for a more streamlined move to digitization in their future. Manufacturers may compare "apples to apples" data, leveraging the resulting analytics across an entire manufacturing network.

42%

of respondents described their facilities as connected, incorporating some automation and integration

Furthermore, designing for digital is a future-proofing measure as far as the labor market is concerned. More than 50% of respondents identified a lack of qualified staff as a challenge to their operations. In higher demand than ever, high quality candidates are selective about their working environments. The modernity of their workspace, the opportunity to work with cutting edge technologies, and a company's demonstrated commitment to keeping up with progress are all draws for high quality candidates.

In addition, standardized modules may enable flexible and remote onboarding of staff virtually or in modular training centers identical to the actual working environment. Meanwhile, modules that support standardized automation lighten the need for staffing altogether. In these ways, supporting digitization through modular design and delivery not only paves the way for smarter facilities and networks, but can also improve a company's recruitment and retention efforts.

Modularization: The measured, mindful path to expansion

Whether an organization is building up or building out, we're seeing a trend of expansion across multiple sites and in some cases, across multiple nations. In this dynamic industry, investment in strategic planning and design upfront is key to keeping expansion moving at pace and on budget. Achieving standardization and consistency across multiple sites isn't an exercise in planning for every single "what if," but rather building agility and adaptability into the design.

Like the aforementioned iPhone, an astute project delivery team understands that a powerful design is one that is both resilient and agile. It offers consistency while supporting ongoing, incremental optimization, based on the needs of its end users. It can adapt as business needs change, scale as new opportunities emerge, and evolve in lockstep with emerging technologies and new ways of working. In the ever-changing life science industry, where patients' lives depend on manufacturers' ability to keep up while keeping control of product quality, standard and modular design is becoming a critical component of future success.

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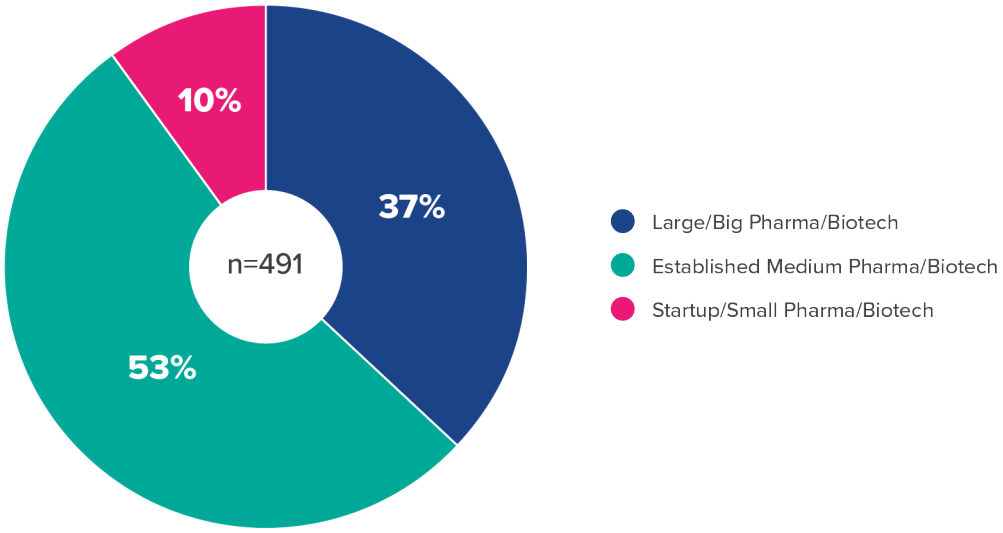
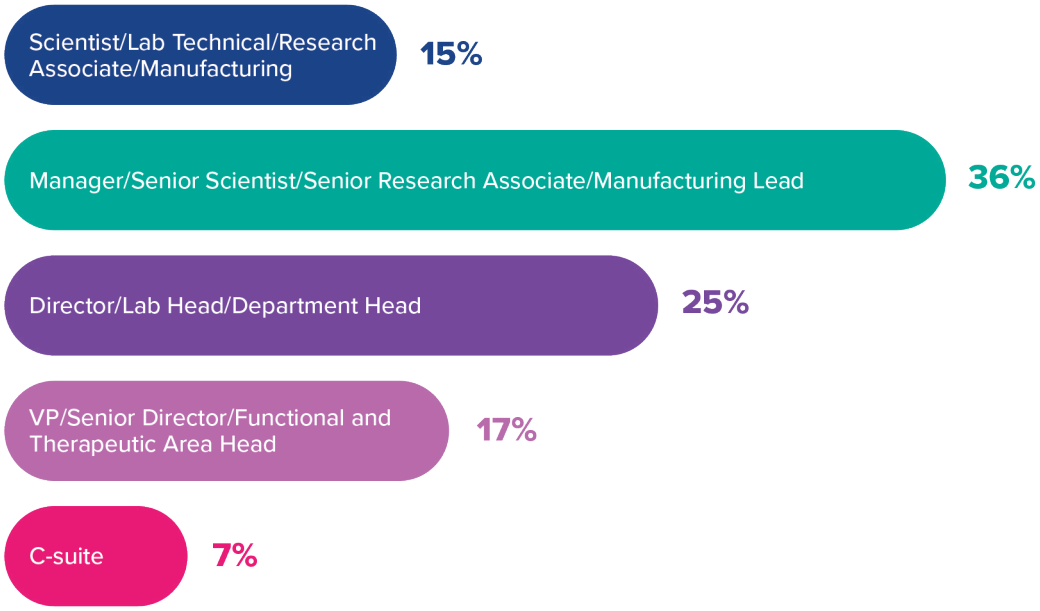
FIRMOGRAPHICS

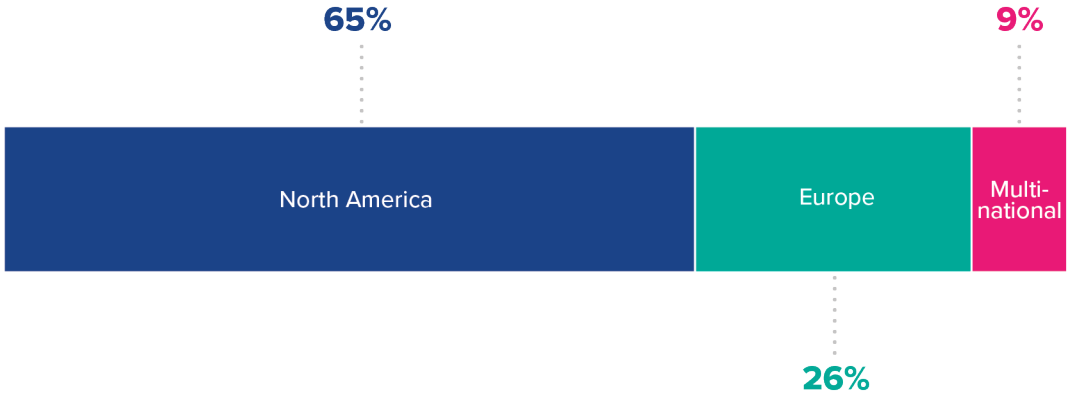
Company Size



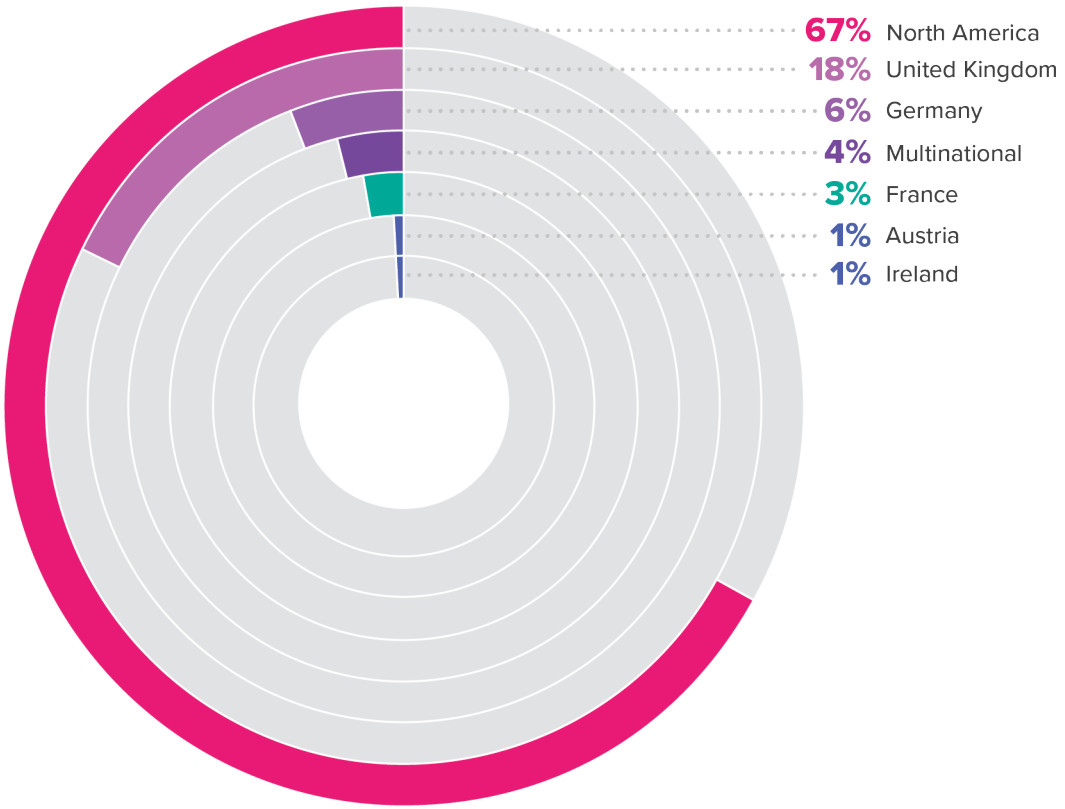
Respondent Role



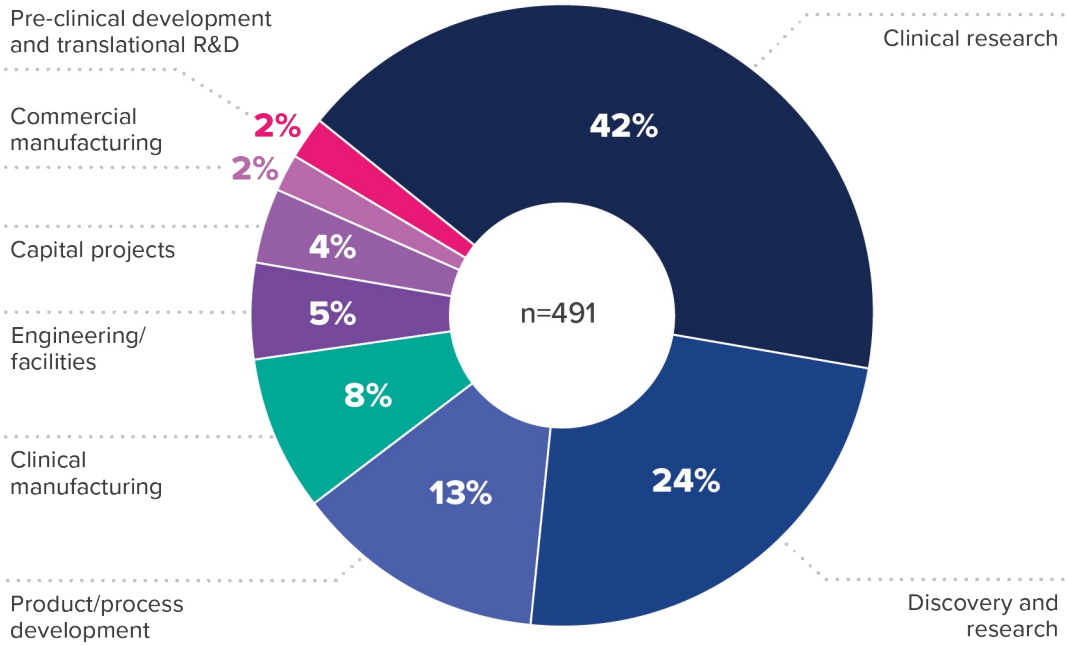
Primary Business Operations



Region of Majority of Working Time



Respondent Job Function



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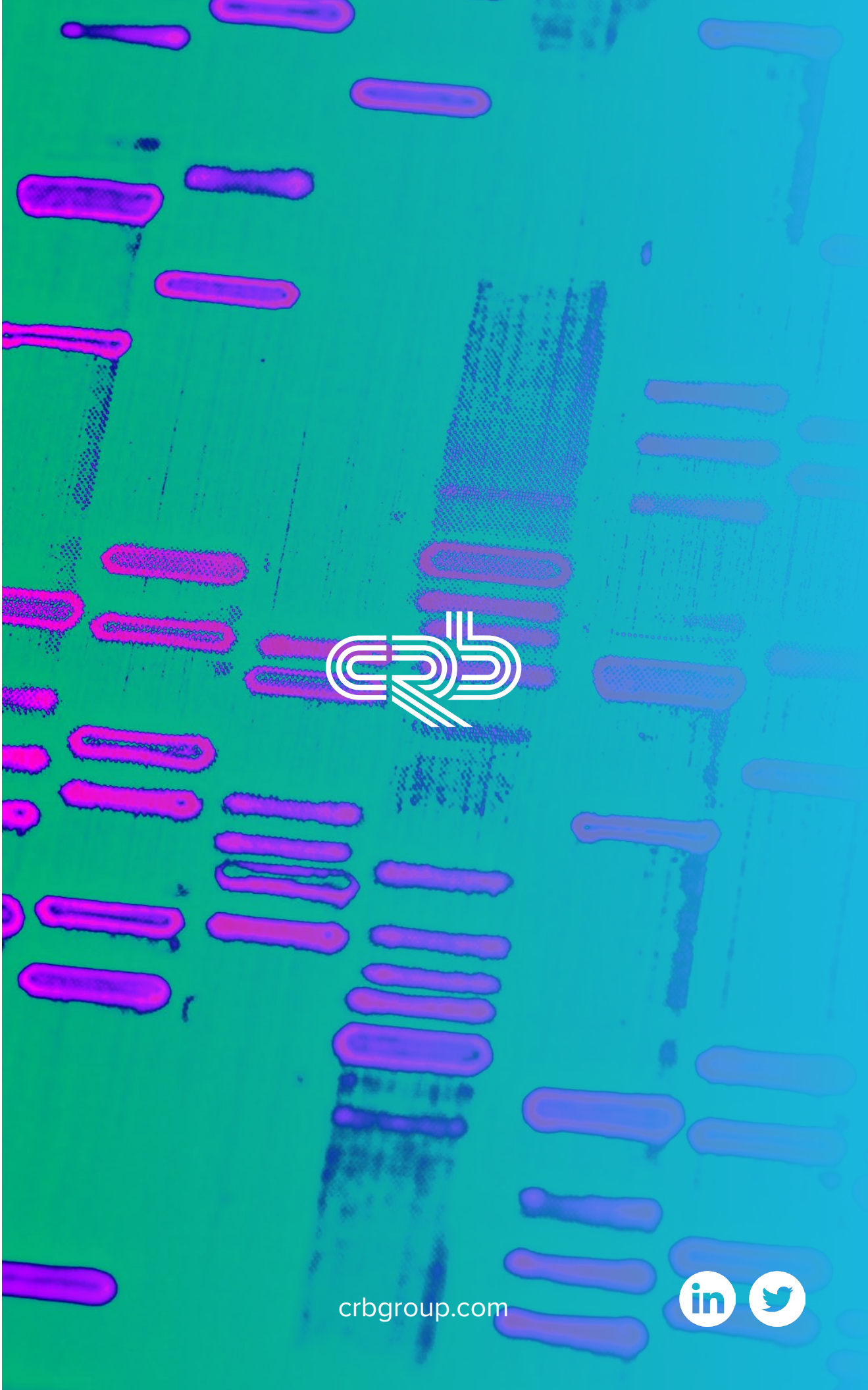

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