2021 Life Sciences

HORIZONS

CLIENT DISCUSSION

About this Report

Everyone has a COVID-19 story. Losing a loved one. Struggling with life in a masked world. We all have our tales of resilience we've faced in our despised "new normal."

These stories have a common theme hidden in the details: disruption. Disruption of life as we knew it in late 2019. Disruption of the public's expectation of cures, vaccines, or therapies. Biopharma leaders are keenly aware of the tally of those disruptions. From upended business models and manufacturing methods to project delivery and digitalization, the world's emerging health threats have put a clock on our ability to respond at scale—quickly, effectively, and safely.

This sense of urgency is captured across the following 100-plus pages of CRB's newest *Horizons: Life Sciences* report. Fueled by survey insights from more than 500 industry leaders, our expert corps of subject matter experts digs deep on the most pressing issues confronting our industry.

From "warp speed" expectations and the revolution of cell and gene therapy manufacturing to Pharma 4.0™, lean project delivery, and sustainability, we pair survey data about today's challenges with analysis that points the way forward.

While it's true that many of those challenges existed before COVID-19, the pandemic exposed their primacy, bringing us daily and heartbreaking reminders about the need for rapid innovation and committed leadership. As Noel Maestre, CRB's Vice President of Life Sciences, notes in his executive summary, "We won't overcome these challenges using the same old tools that served our industry in the past. To succeed, we need the willpower to undertake an honest examination of our industry, our companies, and our facilities, eliminating the systems that no longer work and making room for innovation and reinvention."

CRB is proud to present our survey results to you, and we invite your own reflections about how we meet this important moment in our history. We welcome your feedback through our contact page at crbgroup.com, and we wish you a happy and safe 2022 and beyond.

Tim Barba,
Chief Operating Officer, Global Technical Operations, CRB

Executive Summary:
The dynamic future of life-saving medicine

On changing the way therapies work, and the changing work of making therapies

By Noel Maestre

For the five and a half billion people around the world who have so far received a COVID-19 vaccine, the FDA's 2021 approval of Pfizer-BioNTech's offering may not seem like a big deal. It was available under emergency use authorization before, and now it's here to stay—so what?

For those of us inside the life sciences industry, though, the "so what" is significant. While dangerous variants continue to surge, and drug manufacturers extend their fight against the virus, Pfizer-BioNTech's rapid shift from temporary solution to permanent, branded product is a symbol of good news: like Comirnaty, the gains of our industry's last eighteen months aren't going anywhere.

I'm not only talking about the vaccines themselves, but about everything it took to get us here. New ways of accelerating from R&D to manufacturing. New models for partnership and collaboration. A whole new mindset, which casts off our industry's conservative nature in favor of more innovation, more speed, and more flexibility in the name of more lives saved. We will one day defeat this pandemic, but the waves of change that are overtaking the life sciences are only just gaining momentum.

This survey is our opportunity to raise a periscope above those waves. More than 500 people answered nearly 80 questions, and their collective data revealed two intersecting trends which will define the post-pandemic era for our industry.

The first relates to the science of drug manufacturing. Clinical teams are developing novel therapies capable of preventing and curing diseases that, until now, have eluded effective treatment. We watched this happen in real time as the world's first

mRNA vaccines emerged last year, but this scientific revolution has been in the making since before the pandemic—just look at the scale of private investment in cell and gene therapy research, which reached nearly $20B in 2020. The last eighteen months have only accelerated that trajectory; halfway through 2021, the sector is on track to shatter 2020's funding record with $14.1B already raised. Many of these therapies will achieve regulatory approval over the coming year, further stoking the industry's appetite for scientific innovation.

But for that breakthrough science to mature into sustainable, commercial-scale operations, we need significant changes in drug manufacturing. That explains the second trend running through our survey data: drug developers are rethinking the way our industry operates as a whole.

Dissatisfied with traditional design-bid-build methods and galvanized by the speed of our industry's pandemic response, many project leaders are turning to much faster and more agile solutions. They're leveraging the predictive capabilities of AI and machine learning to build smarter, more secure, and future-ready manufacturing centers. And they're redesigning the traditional GMP cleanroom to accommodate closed and automated processes—a necessary step toward improving the cost and quality of tomorrow's medicines.

With these macro shifts underway in both the science and the practical realities of drug manufacturing, what's happening at a more micro level—the level of on-the-ground decisions that today's companies make every day, around the world? To answer that question, we've carved this report into eight key focus areas.

CELL AND GENE THERAPIES

In this article, expert Peter Walters looks at what cell and gene therapy developers can do to plan for long-term commercial success while so much change is underway at the lab bench. Drawing from our survey data, Walters takes a close look at how technologies like single-point, process-in-a-box systems will transform the future of drug manufacturing.

OLIGONUCLEOTIDES

After decades of research, the science of oligonucleotide manufacturing is on the brink of graduating from the lab bench to the bedside—and once it does, it will change many patients' lives. That's why nearly a quarter of our survey respondents have oligo therapies in their pipeline, or are planning to add them in the near future. What challenges will these companies face as they approach commercial

manufacturing? Join experts Bill Jarvis, Jim Love, and Brendan Nichols for their perspective.

RNA TECHNOLOGIES

The pandemic thrust mRNA technology into the spotlight, rapidly catalyzing years of research into life-saving vaccines. But as our survey data shows, that's just one slender chapter in a complex story. More than one-quarter of respondents are pursuing or plan to pursue RNA therapies across a wide array of indications, from autoimmune diseases to oncology. As their pipelines mature, these companies face new questions about supply chain management, facility design, and scale-up. In this article, experts David Estapé, Ken Jacobson, Can Aktar, and Jake Adams examine these questions and help readers understand where the future of commercial RNA manufacturing may take us.

PHARMA 4.0™

Four-fifths of our survey respondents identify their company in the top three tiers of the five-level Digital Plant Maturity Model (DPMM), and most aspire to Level 4, defined by digital facilities that leverage predictive analytics. What stands in their way and how can companies plan around those barriers to unlock the full potential of AI and machine learning? In this article, experts Yvonne Duckworth, Niranjan Kulkarni, and Matt Edwards answer that question.

WARP SPEED DRUG DELIVERY

What began as a rallying cry to ignite our industry's rapid pandemic response is now a permanent feature of drug delivery—warp speed, in other words, is the new cruising speed. In fact, our survey reveals that "speed-to-market" jumped from a lower-ranking business driver before the pandemic to the top priority today, overtaking cost-based considerations by a healthy margin. Experts Dominic Tate, Christa Myers, and Jarrod Wrampe explore what this "warp speed" state of mind means for companies planning their commercial scale-up strategies.

LEAN DELIVERY

When we asked about project delivery, we noticed an interesting schism: most say that they rely on design-bid-build or design-build, and yet, in the next question, they ranked those very delivery methods as least satisfactory compared to more lean and integrated models. What's going on? Experts Mike Barrett and Carl Rohs dive into our survey data to find out, and to help companies better match their project delivery approach with their need to move fast and maintain quality.

PPMOF

At CRB, we often rely on lean tools like PPMOF (prefabrication, preassembly, modularization, and offsite fabrication) to help clients meet aggressive delivery milestones. But what about the rest of the industry? Through this survey, we learned that while 70% of companies say they're using PPMOF optimally, only a small minority consider it valuable. Chief among our respondents' concerns: quality and cost. So, what are the facts? Can PPMOF help meet all project delivery criteria, not just speed? JP Bornholdt and Dennis Kearney provide their expert perspective in this article.

SUSTAINABILITY

Moving from chronic treatments to one-time curative therapies is our industry's next big innovation, but if we're destroying our planet in the process—well, where does that leave us? That's why it's encouraging to see that the majority of respondents have a sustainability strategy in place. But how are different organizations using that strategy to balance the needs of the planet, the people inside their company, and their bottom line? Join experts Jeff Wegner and Maya DeHart for a deep dive on this topic.

CLIENT DEEP DIVE: JOHNSON & JOHNSON

Meet Jim Breen, VP Lead Biologics Expansion, Janssen Pharmaceutical Companies of Johnson & Johnson. In this article, Jim reflects on his own answers to our survey questions, giving readers a rare glimpse inside one of the world's leading life science innovators. You'll learn about Johnson & Johnson's approach to moving fast, managing constant change, and maintaining a strong and resilient company culture along the way.

Disruption—the harmonizing theme

Those of us who rolled up our sleeves for an mRNA COVID-19 vaccine this year may do the same for an mRNA cancer vaccine in the future. Parents will soon be able to screen for and prevent DNA risks in their children. Those whose diseases would have once shortened their lives will have access to genetically engineered therapies that could eliminate their diseases altogether. This is the future of life sciences.

These revolutionary ideas promise effective therapies and sustainable new business models, but they also introduce all-new challenges. We won't overcome these challenges using the same old tools that served our industry in the past. To succeed, we need the willpower to undertake an honest examination of our industry, our companies, and our facilities, eliminating the systems that no longer work and making room for innovation and reinvention. Instead of slow and incremental change, we need bold action. Instead of outdated checks and balances, we need delivery strategies that balance risk with progressive new ideas. Instead of competition, we need collaboration. This is how we will prepare ourselves for what's to come. It's the only way.

In that spirit of collaboration and progressive thinking, our team offers you this report, which consolidates the experiences and perspectives of so many from across our industry as they face a new horizon in drug manufacturing.

Emerging Advanced Therapies

SECTION ONE

Small Scale, Big Revolution:

The future of cell and gene therapy manufacturing

By Peter Walters

Among the waves of innovation that have disrupted cell and gene therapy (CGT) manufacturing over the past ten years, two have reached tidal heights. The first came in 2017, when the FDA approved the world's inaugural genetically modified cell therapy.

The second is underway.

Propelled by year after year of record-setting investments and regulatory approvals, innovators in this category are on track to revolutionize the way our world approaches medicine—not as a chronic treatment for illness, but as a one-time cure. What happens next will result from the monumental effort of the last decade, and will define the decade to come.

To better understand what this means in practical terms for today's cell and gene therapy manufacturers, we asked our survey respondents to tell us:

WHAT'S HAPPENING RIGHT NOW?
Companies are shifting away from autologous cell therapies toward more commercially viable allogeneic products.

WHAT WILL HAPPEN NEXT?
Closed, automated, single-equipment platforms are emerging as a promising alternative to high-cost and inefficient open processing.

WHAT'S NO LONGER HAPPENING?
Compared to a year ago, survey respondents have embraced their gene technologies of choice, and are less likely to switch in the future.

THE INDUSTRY IS SHIFTING TO COMMERCIALLY VIABLE ALLOGENEIC PLATFORMS

If efficacy was the only success metric that mattered in the race toward curative medicine, autologous cell therapies—that is, patient-specific therapies—would own the podium. Take patient-specific CAR T-cell therapies, for example: ten years of clinical data prove that a single dose of these precisely engineered immune cells can eliminate certain targeted cancers. From that perspective, autologous cell therapy is a magic bullet.

But for a disruptive new drug to make the leap from niche to mainstream, it needs a scalable manufacturing pathway. That's where the bright promise of autologous therapies loses its shine. To extract, transport, engineer, expand, and reintroduce patient-specific cells safely and consistently, companies currently rely on open, labor-intensive tracking, manufacturing, and quality testing processes. Making these processes work in a lab is one thing, but how will you get individualized therapies to the millions of people who ultimately need them?

Our survey respondents are exploring a potential answer by unshackling themselves from small, patient-specific batches and moving instead toward allogeneic (donor-based) therapies (Figure 1). Dig a little further, and we can see that this is especially true for companies new to drug development; while nearly a quarter of large biopharma companies and CDMOs say their portfolio includes autologous cell therapies, only 12% of respondents from the start-up community fall into this category (Figure 2).

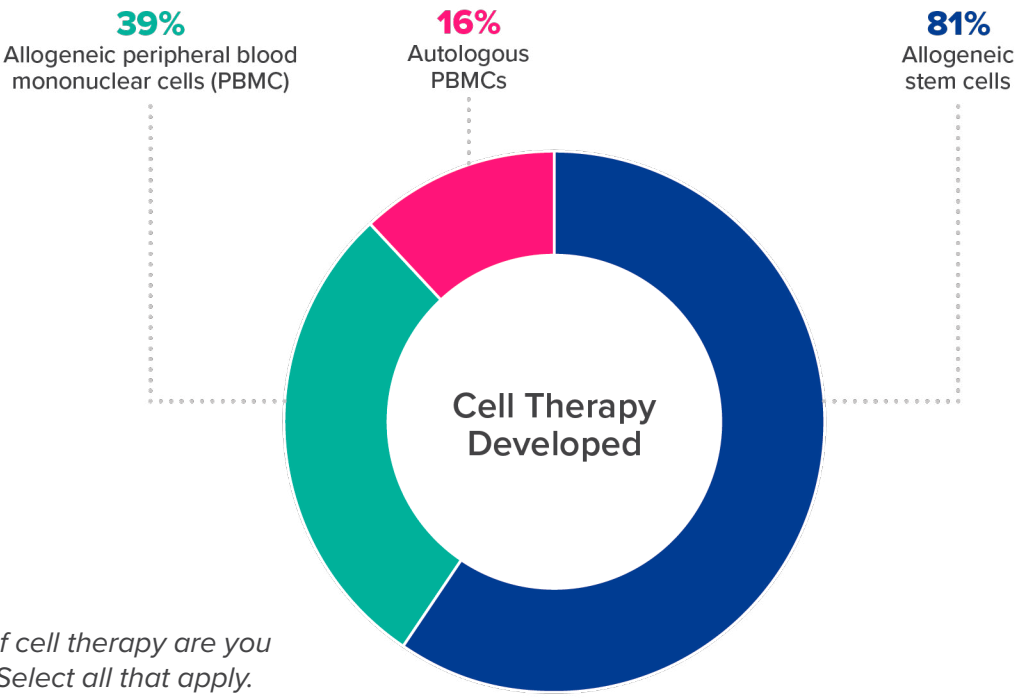


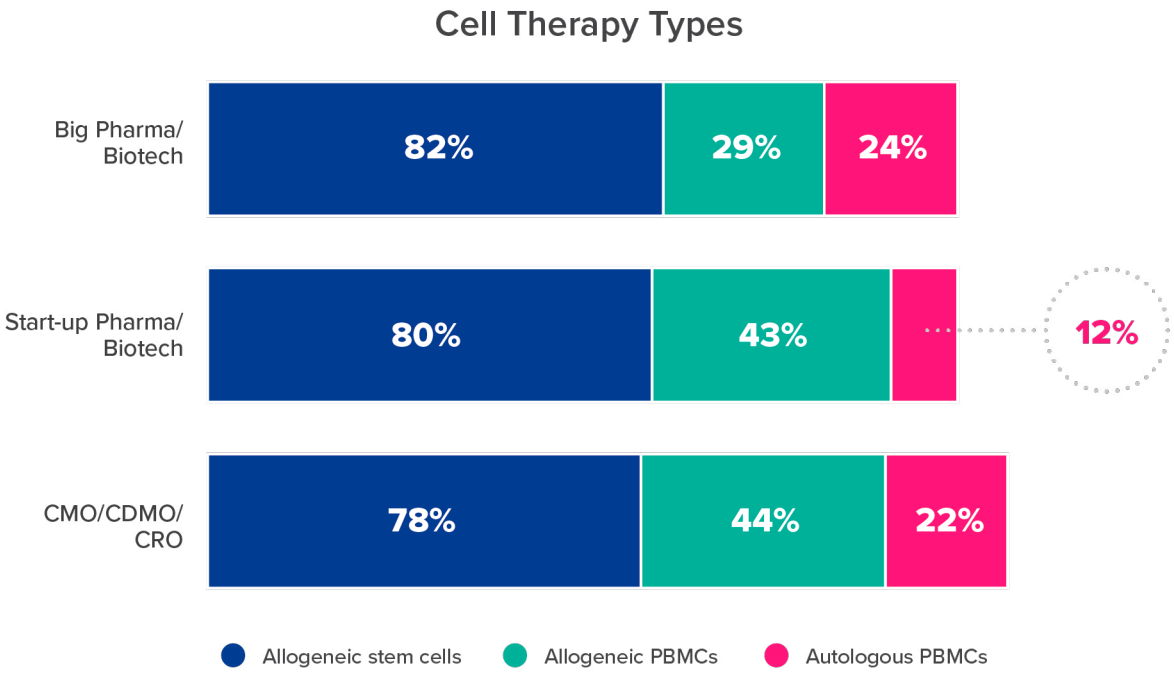
FIGURE 1

What types of cell therapy are you developing? Select all that apply.

Source: CRB

FIGURE 2

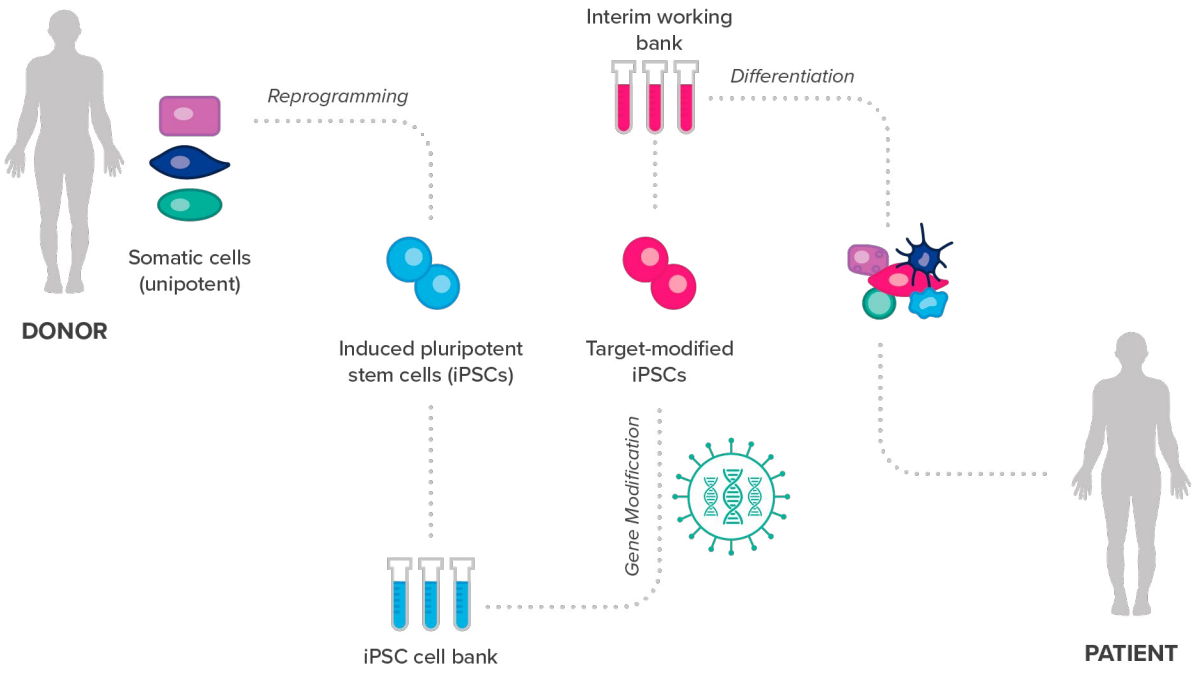
What types of cell therapy are you developing? Select all that apply.



Source: CRB

This is likely because most large companies reached the mecca of cell therapy development through acquisition, rather than through their own internal research pipeline. These large companies understood the potential of cell therapies early on, and were quick to get their foot in the door by investing in the sector's first and most promising pioneers—many of whom, at the time, would have been developing patient-specific products. That could explain why autologous therapies are overrepresented among larger companies, while today's start-ups can focus their research on more versatile allogeneic alternatives.

In fact, versatility is the reason why allogeneic stem cell therapy manufacturers as a whole are most likely to rely on induced pluripotent stem cells (iPSCs) as their starting material, as depicted in Figure 2. Like shaking an Etch-a-Sketch, manufacturers are able to take almost any type of living donor cell and, through an induction and reprogramming process, wipe it clean of the attributes that differentiate it. What's left are "blank slate" (or pluripotent) stem cells, which can be weaponized against specific diseases and then differentiated into almost any other cell type in the body, for almost any patient (Image 1).

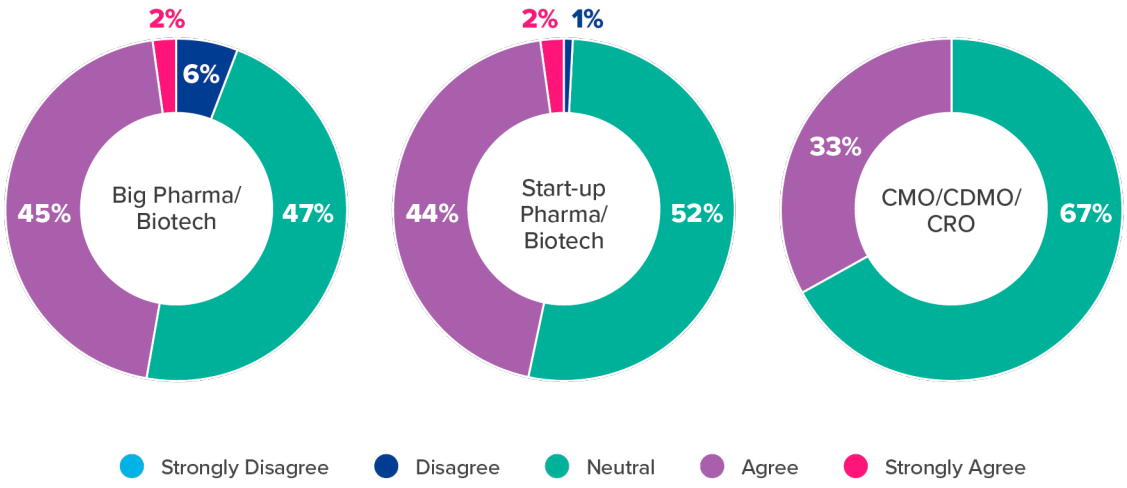


In this allogeneic approach, manufacturers are no longer manually manipulating the compromised immune cells from a sick individual—instead, they can leverage scalable cell platforms and established manufacturing technologies from traditional biopharma to create banks of healthy, donor-sourced material, genetically edited in a more controlled fashion and ready to propagate into large volumes of therapies.

And yet despite this commercially viable alternative, roughly half of survey respondents from both large biopharma companies and smaller-scale start-ups are neutral on the question of moving away from autologous therapies. For CDMOs, that proportion climbs to 67% (Figure 3). Why keep two dogs in the race, when one is so clearly the winner?

FIGURE 3

Do you anticipate your company moving away from autologous cell therapies in the next 5 years?



Source: CRB

The answer may lie in what allogeneic therapies don't have, at least not yet: years of data to prove their efficacy. This is still a nascent category, and we simply don't know if or when allogeneic therapies will perform as well as proven autologous therapies. Take, for example, an allogeneic immuno-oncology therapy that relies on genetically modified cells. Lab-based results are one thing, but how well will this therapy perform in the "uncontrolled lab" of the human body? These unknowns leave drug developers with a difficult decision: should they invest in a product that is effective but notoriously difficult to manufacture, or a scalable product that doesn't yet have substantial clinical data to back it up? Our survey respondents may simply be waiting to see which way this question will tip before investing heavily in the appropriate clinical and commercial manufacturing systems.

Key takeaway:

As technologies improve, so will the payoffs of both autologous and allogeneic manufacturing.

The technology supporting donor-based cell therapies is continuously improving. Developers are mastering its potential to not only weaponize immune cells, but to produce genetically edited lung cells, pancreatic cells, cardiac muscle, and more. As the industry learns more about tapping into this powder keg of curative and regenerative potential, a shift in this data is expected, with more companies embracing a move away from autologous manufacturing.

That's not to say that autologous therapies are history. The technology best suited for this type of manufacturing is also on the cusp of a significant leap—one that flips the script on small-scale, personalized therapy production, turning its greatest burdens into advantages.

PROCESS-IN-A-BOX SYSTEMS WILL TRANSFORM CGT MANUFACTURING

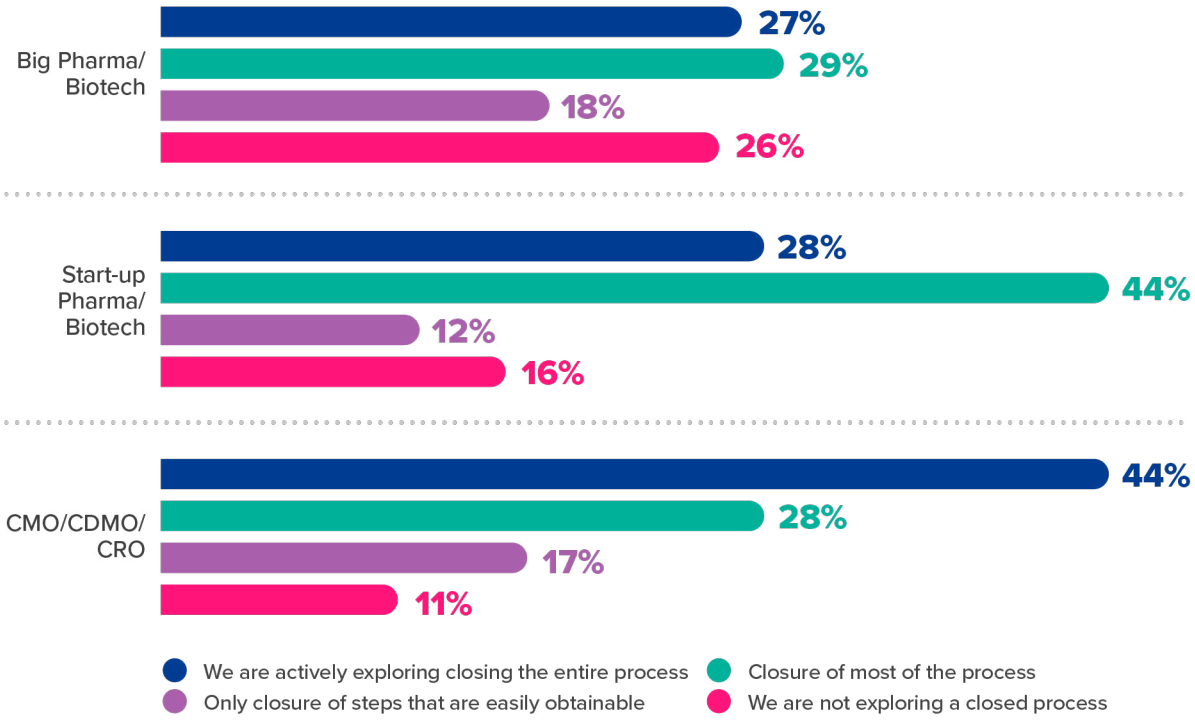
The big hurdle facing manufacturers of patient-scale therapies is cost, which is a function of its open and aseptic process. Scaling that process to accommodate a large patient population requires expensive square footage, for cleanrooms and for the ancillary spaces that keep those cleanrooms sterile, like segregated corridors, gowning areas, and airlocks.

That's why so many of our survey respondents are moving toward process closure (Figure 4). Some are closing the easiest steps first. Others are pushing hard to close their entire process, especially CDMOs who likely realize that investing in closed, automated processes will mean greater capacity, faster throughput, and more clients in the long run.

The majority of our survey respondents sits somewhere in the middle of this spectrum, particularly those from start-up companies. They can see the commercial benefits of process closure, but there's no single solution to get them there. That's because today's off-the-shelf systems carry a significant asterisk: they can close *most* of your process, but usually not all of it.

FIGURE 4

To what extent is your organization actively pursuing closure of your process?



Source: CRB

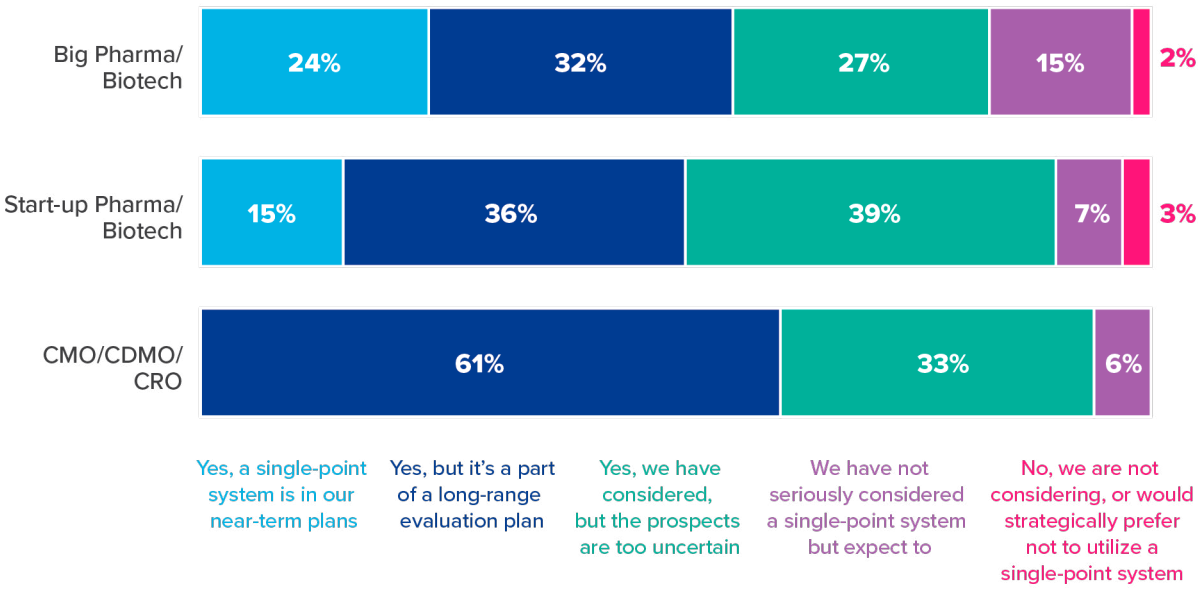
If two or three steps need to happen outside of your closed system, what's to gain by closing it at all? The answer to that question is everything. Integrating a closed processing system today, even if that means investing in a design, will put you at a huge advantage in the future when those bespoke designs become templates for mainstream cell and gene therapy production. By working with vendors to close their process from the start, companies who are actively pursuing this option are setting themselves up for a denser, much more economical use of their facility footprint—a decision that will reward them over the long term.

But this is only the first step toward a much larger shift that's coming, a shift that will disrupt everything we know about cell and gene therapy manufacturing; specifically, end-to-end, single-point, process-in-a-box platforms.

Every type of company represented in our survey shows serious interest in this type of revolutionary manufacturing system (Figure 5). Large companies are more likely to adopt it in the near-term, perhaps because they have the resources and the risk tolerance to explore the bleeding edge of technological innovation. Start-ups are slightly more cautious. This could be because they're under pressure to move through clinical research and into the marketplace as fast as possible, and they aren't (yet) focused on how to sustain commercial production once there. But they should be; by aligning today's lab-scale activities with a future process that leverages single-equipment technologies, they'll be much better positioned to outpace competitors and run a dense and financially resilient manufacturing pipeline down the road.

FIGURE 5

Has your organization considered a single-equipment closed automated processing system, often referred to as a "process-in-a-box"?



Source: CRB

The big promise of process-in-a-box systems is that they could eliminate the cleanroom altogether, pushing segregation entirely to the equipment level. For those with autologous cell therapies in their pipeline, this is game-changing. Manufacturers could scale out by densely stacking large volumes of these closed and automated systems inside a warehouse, making maximum use of every square foot and greatly reducing their labor costs while continuing to focus on small, individualized product batches.

Process-in-a-box systems could revolutionize allogeneic cell therapy manufacturing, too. We have already highlighted the possibility of leveraging equipment platforms from traditional biopharma to drive economies in donor-based therapy production, but that approach is not without its challenges. Manufacturers have just one hour to fill, inspect, and freeze cryo-formulated therapies before cells begin deteriorating, for example. That's easy to do with a few samples in the lab—much harder when you're filling thousands of vials. If these manufacturers could make a commercial success of scaling out with small batches (versus scaling up with large volumes), they could solve many of these operational complexities.

Key takeaway:

The process-in-a-box approach could revolutionize cell and gene therapy production in the next five years. To reap its commercial rewards, start planning now.

As process-in-a-box platforms mature, the distribution in Figure 4 will change; those in the consideration stage will soon shift to embrace these all-in-one platforms, and the rest will be forced to rethink their approach or get left behind.

Wherever you fall across that adoption continuum, the best thing you can do for the future of your operation is to adopt a "commercial state of mind." That means assessing every decision you make today against where you plan to be tomorrow, with a perspective on how technologies are changing and what that means for your future manufacturing process. That way, you will arrive at the threshold of a commercial launch with a scalable process and a flexible, innovation-ready manufacturing strategy.

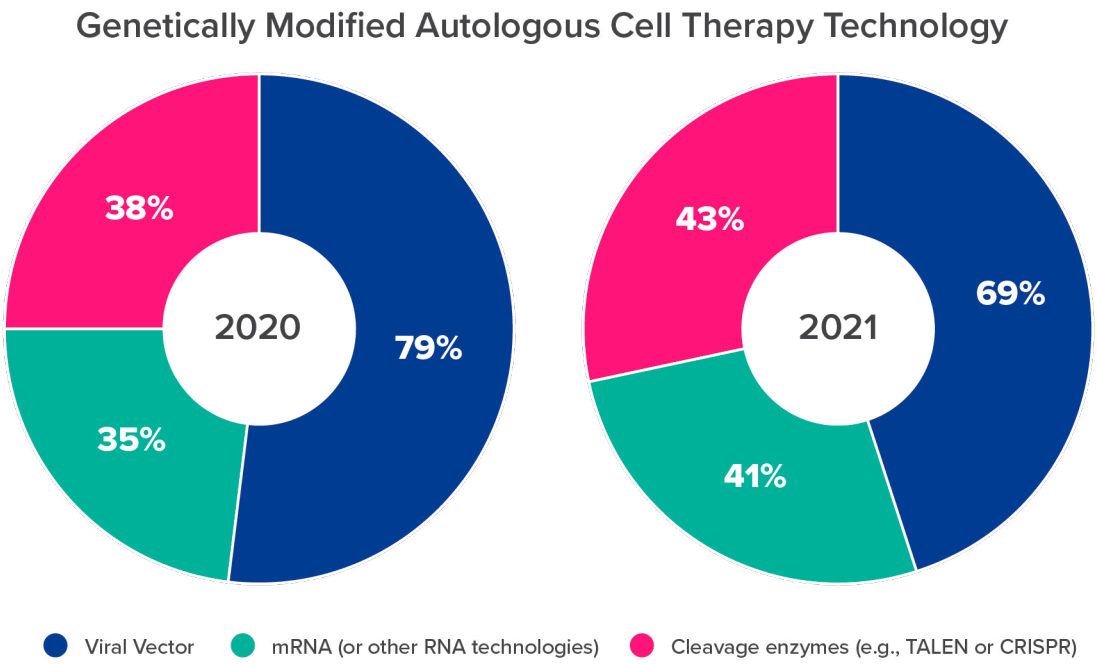
MANUFACTURERS HAVE SETTLED ON A TECHNOLOGY STRATEGY. WILL THEIR CHOICE PAY OFF IN THE FUTURE?

In 2020, as the pandemic's earliest waves swept the globe, we asked cell and gene therapy leaders to tell us about their strategy for choosing between gene-modifying technologies. We published their answers in our inaugural Horizons report. One year later, we asked the same question—and got a notably different result.

Although the distribution of gene technologies is roughly the same (Figure 6), just 19% of respondents felt committed to their chosen technology one year ago (Figure 7). Today, that number has climbed to 80%.

FIGURE 6

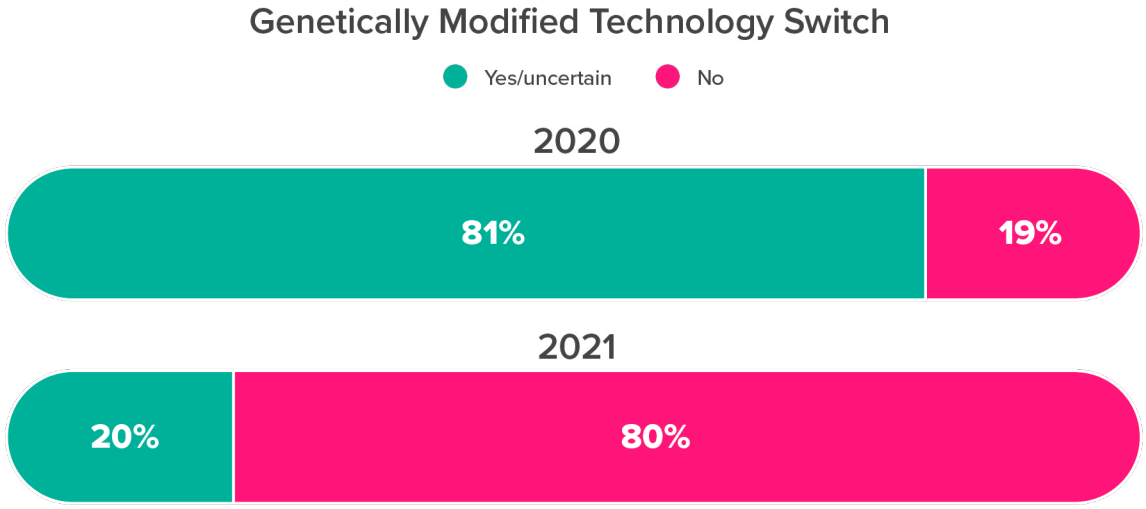
What gene technologies are you using now to produce genetically modified cell therapies? Select all that apply.



Source: CRB

FIGURE 7

To what gene technologies do you anticipate switching? Select all that apply.



Source: CRB

This tells us that the successive cycles of innovation that have defined the last few years of cell and gene therapy manufacturing are beginning to settle, without (yet) yielding a single golden chalice. Each technology introduces unique challenges and opportunities, and manufacturers are growing more comfortable with these nuances and the accommodations they require.

Viral vector manufacturing, for example, is the most established and well-understood of these technologies, but it's difficult to scale because of transfection challenges and issues related to containment and segregation. The race for a SARS-CoV-2 vaccine, meanwhile, has thrust mRNA into the global spotlight, and many manufacturers are relying on the versatility of this technology to target a wide range of indications. Then there's clustered regularly interspaced short palindromic repeats (CRISPR), exalted in the media for its potential to precisely edit the human genome. But it was only a year ago that researchers injected a CRISPR gene therapy into the human body for the first time, and while the result was promising, we're a long way from seeing approved, commercial-scale CRISPR therapies in action.

With all three technologies offering such different advantages and risks, the real question has shifted from, "Which will you choose?" to "How will you leverage your chosen technology to drive commercial outcomes?" In practice, this means you should focus on a single technology to fuel your whole product pipeline, instead of using an mRNA platform for cell therapy over here and viral vectors for vaccine research over there. By building these technological synergies into your manufacturing strategy, you can leverage the same talent pool, facility layout, equipment platforms, supply chain inputs, and other resources for as many products as possible, without handcuffing your company to a CMO or having to fund incompatible capital projects.

Key takeaway:

Think about your chosen technology not only as an R&D driver, but as a key component of your long-term business strategy. How will it drive internal synergies in your process?

For lab-scale start-ups trying to mitigate risks and deliver on their promise to investors, the temptation to bet on divergent gene technologies is strong. But aligning the technologies in your lab with your business strategy will make future scale-up much easier and more cost-effective. This is how tomorrow's cell and gene therapy leaders are distinguishing themselves today.

Toward the next frontier

Like astronauts, cell and gene therapy innovators are programmed to explore new territory—but instead of the vastness of outer space, they focus their attention on the world's tiniest living matter. Getting it right means getting curative therapies to patients with no other hope of surviving their illness.

This is the great promise of cell and gene therapies. As disruptive new technologies and scientific approaches to small-scale, commercially viable manufacturing emerge over the next five years, we're on the cusp of making that promise a reality for more patients than ever.

Synthesizing Success:

Oligonucleotides could transform medicine. Are manufacturers ready?

By Bill Jarvis, Jim Love, and Brendan Nichols



After years of research, the field of oligonucleotides finds itself entering adolescence. Investors are lining up. Research pipelines are maturing. And the first approved medicines are making their way onto the market—a clear sign that oligonucleotides are hitting a growth spurt. But with growth, come growing pains. Here's where we think the field is headed, and what manufacturers will need to navigate along the way.

WHAT'S CONSIDERED AN OLIGONUCLEOTIDE?

As a term, "oligonucleotide" encompasses many technologies. The field and its applications grow more diverse every year. Currently, technologies primarily include:

- Small interfering RNA (siRNA) - double-stranded RNA that inhibits gene expression via degradation of mRNA in the cell
- Aptamers - short and single-stranded oligos that bind to target proteins and alter their function
- Single guide RNA (sgRNA) - used in CRISPR-Cas9 systems
- Antisense RNA - short RNA complementary to mRNA that blocks translation

Oligos differ from mRNA therapeutics in terms of the diseases they treat and the way they are manufactured. Oligos are chemically synthesized while mRNA is made via in vitro transcription (IVT).

A DEVELOPING FIELD

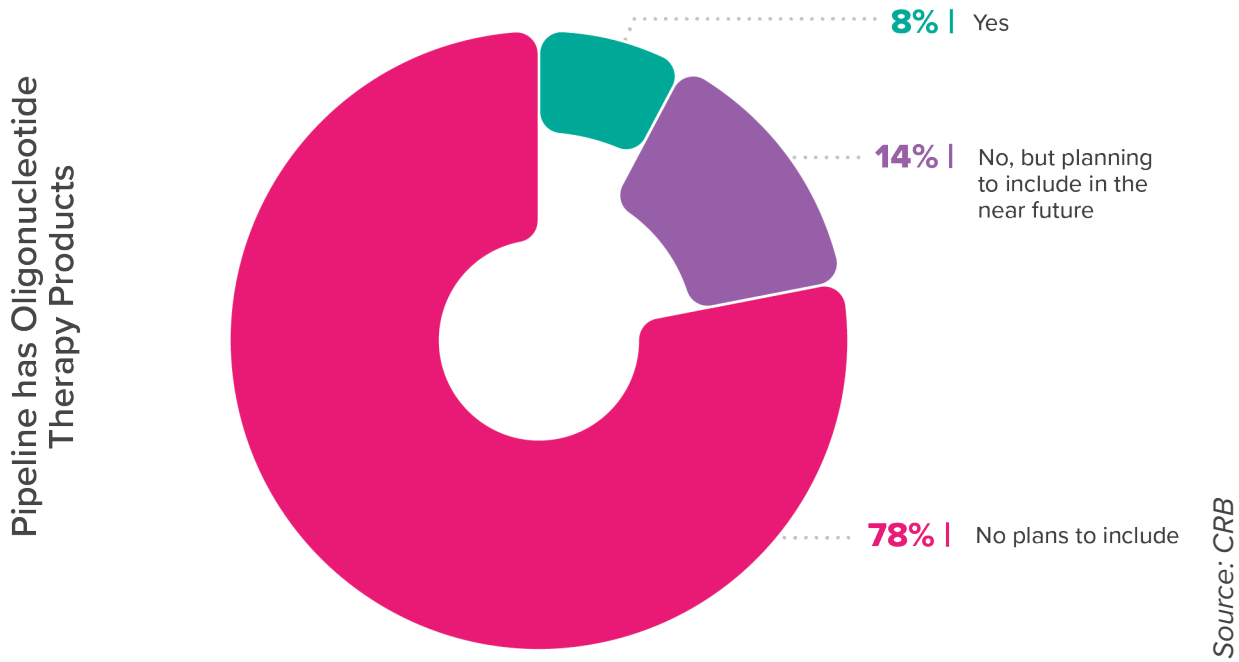
Based on survey responses, 8% of pharma manufacturers have oligonucleotides in their pipeline, and 14% plan to incorporate them in the near future (Figure 8). Of these manufacturers, more than 60% are only just entering (or are planning to enter) the space today (Figure 9). Biotech startups make up the largest share, 74%, of this incoming population (Figure 10); however, large pharmaceutical manufacturers could also make a large contribution to the field with their involvement expected to double. (Figure 11).

14%

of respondents plan on incorporating oligos into their pipeline in the near future

FIGURE 8

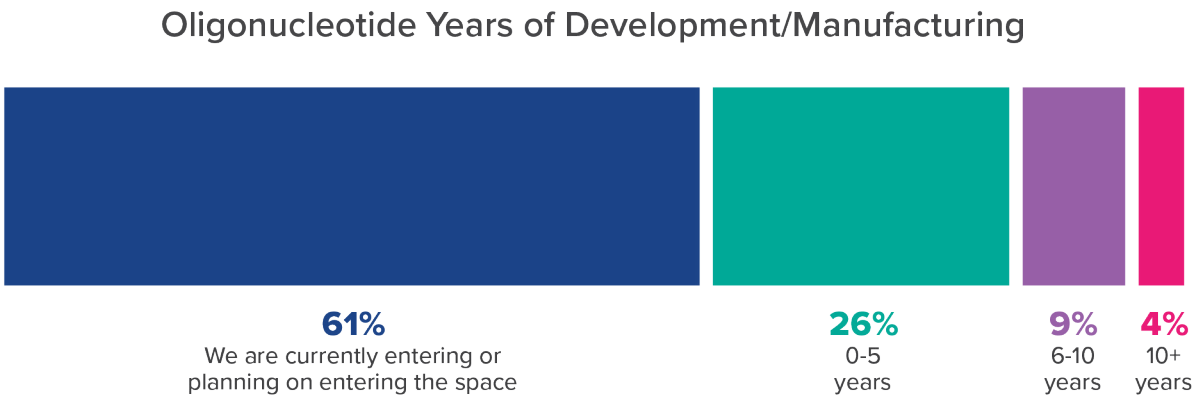
Is your company's pipeline comprised of oligonucleotide therapy products?



Source: CRB

FIGURE 9

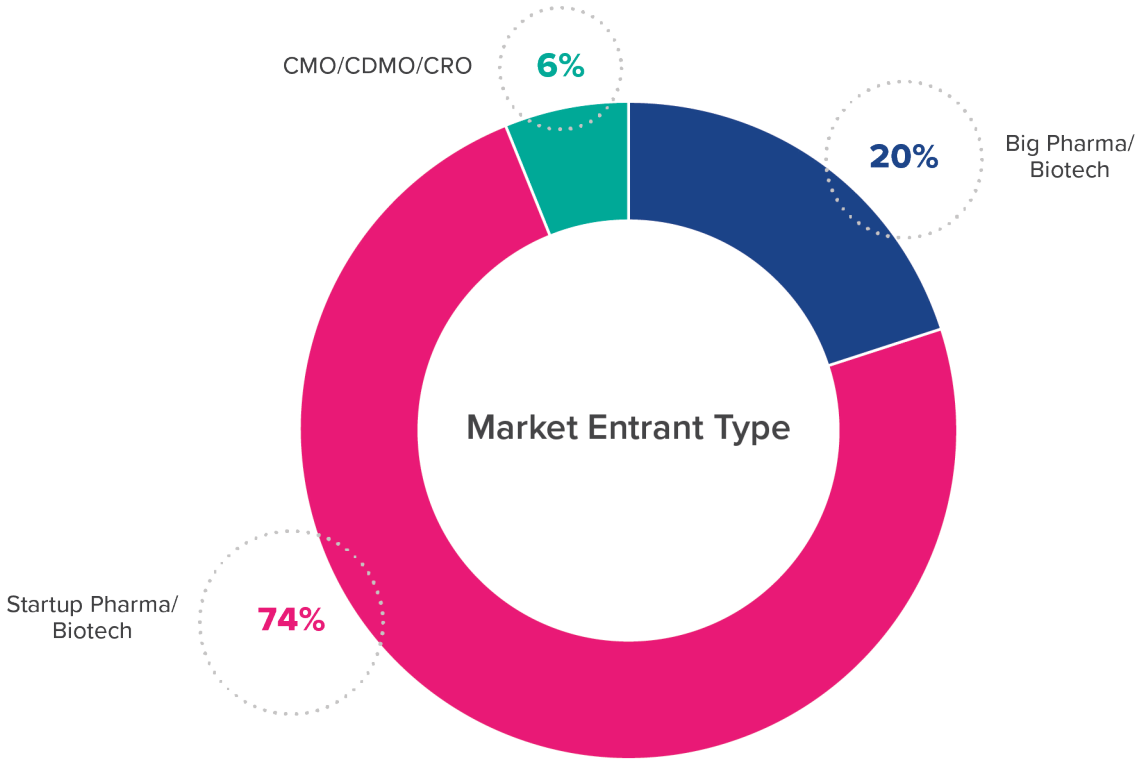
How many years has your company had oligonucleotide development or manufacturing?



Source: CRB

FIGURE 10

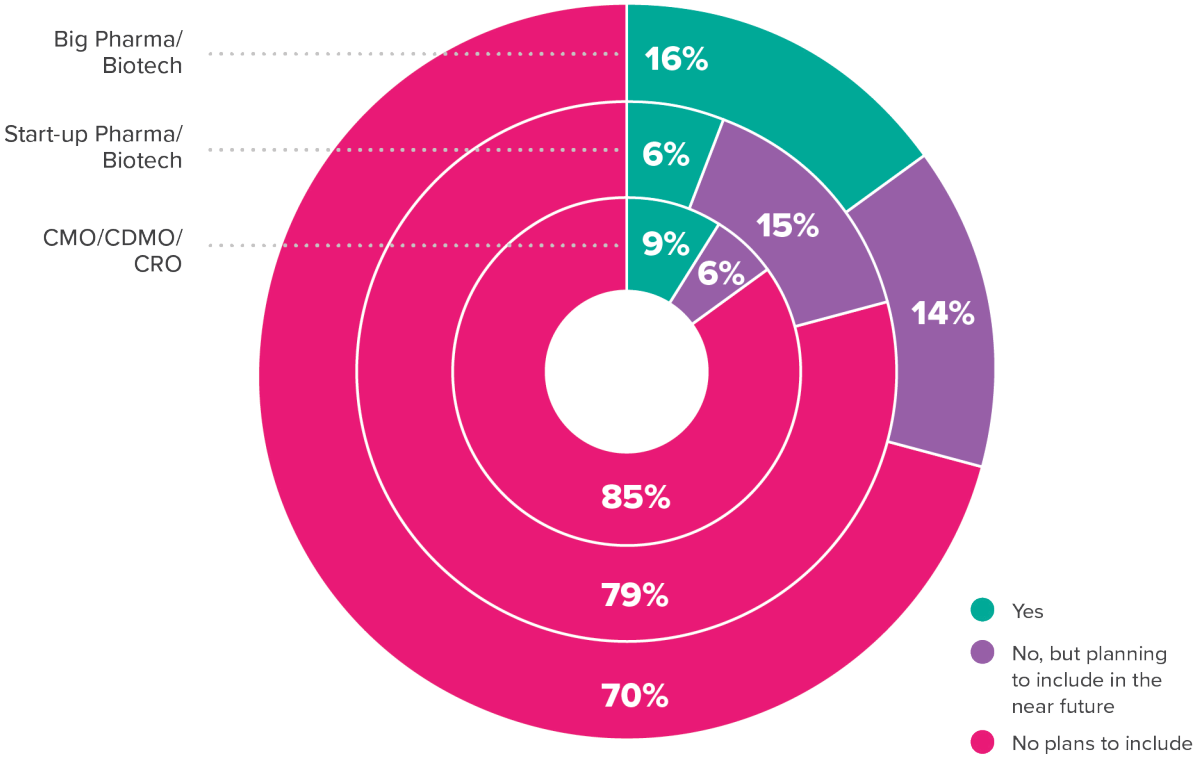
Of the 14% in Figure 8 who answered no, but plan to include oligo development in the future, nearly three-quarters were startups.



Source: CRB

FIGURE 11

Is your company's pipeline comprised of oligonucleotide therapy products? (deep dive)



Source: CRB

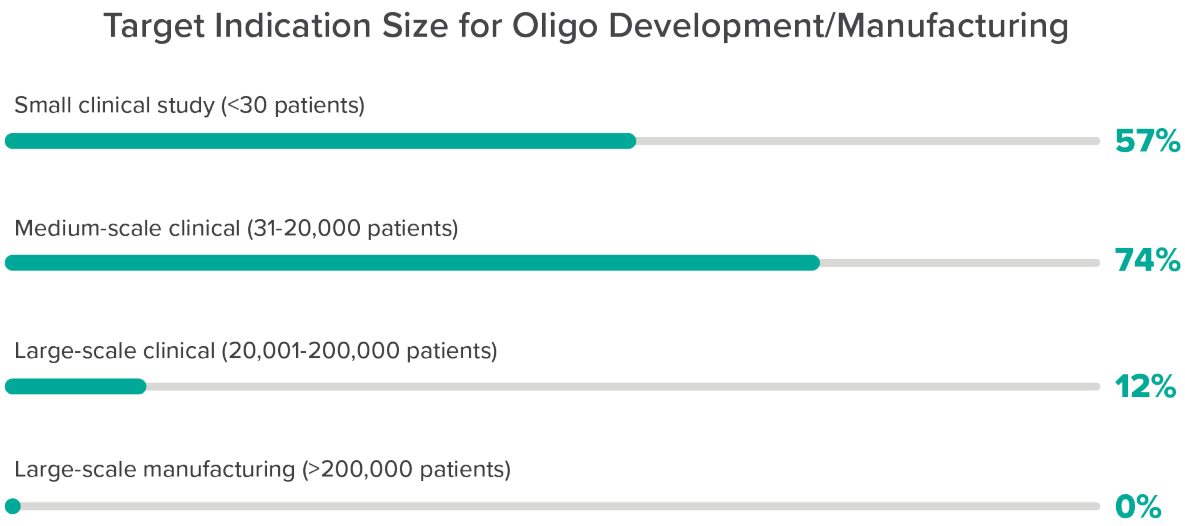
With most survey respondents just entering or planning to enter the field, we wanted to know how they saw their future R&D and manufacturing pipelines. Were they planning to target indications with large or small patient populations? For most respondents with oligos in their future, the answer is "somewhere in the middle"—three-quarters are targeting indications with a patient population between 31 and 20,000. Just 12% are focused on larger-scale indications (Figure 12). This significant focus of oligo development and manufacturing underscores the potential for oligonucleotides to reach small patient populations and unique indications.

Just 12%

of respondents are focused on larger-scale clinical indications

FIGURE 12

What is your target indication size for your oligo development or manufacturing?



Source: CRB

TACKLING MORE ILLNESSES

What is behind such a significant push in oligonucleotide development and manufacturing?

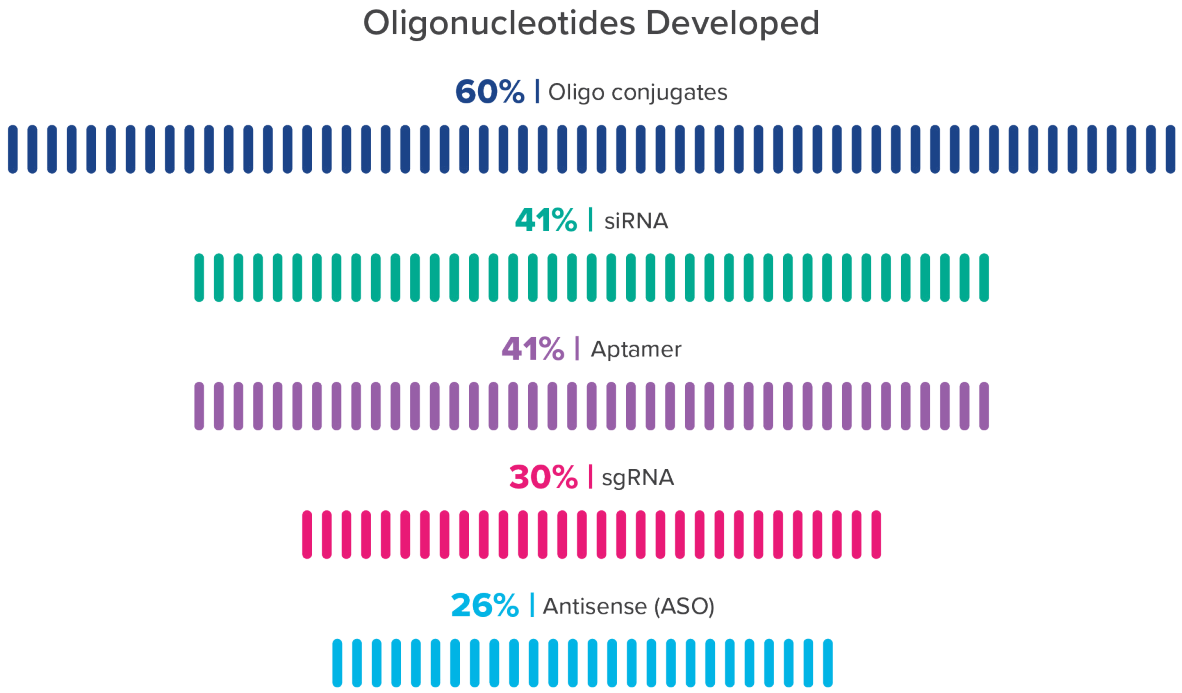
Oligonucleotides stand to blossom as a tool for very effective and potentially curative therapies. The field holds the promise of medications offering better tolerability and dosing regimens, higher clinical efficacy, and the ability to treat some diseases for the first time.

Companies are looking to use oligos to address areas currently lacking therapies and may even find oligos that better address well-researched illnesses and replace existing therapies. Researchers are leveraging their greater understanding of the human genome for clinical benefit through the development and production of novel oligonucleotide therapeutics.

Because of the breadth and enormous promise of oligos, companies are spreading their research across a wide range of oligo types. The majority of respondents are developing and/or producing oligo conjugates (60%), while at the same time siRNA, aptamers, and sgRNA products are also garnering substantial interest (Figure 13). Conjugated molecules are launching oligonucleotides into the realm of nerve-based indications, such as ALS. Other indications being researched include Alzheimer's and muscular dystrophy. Ultimately, oligonucleotides could end up serving as treatments for almost any genetic disease, including cancers.

FIGURE 13

What types of oligonucleotides are you involved in developing and/or producing?



Source: CRB

While the science of oligonucleotides is evolving, so are the methods used to deliver these therapies safely and effectively into the body.

Recent progress has resulted in more stable molecules that, in some cases, remain pharmacologically active for months; this has made oligonucleotides more practical as therapeutics. Previously, the half-life of these molecules within the body was so short that maintaining therapeutic levels required daily injections. Recently, there has been an uptick in research attention given to base modifications such as bridged nucleic acids (BNAs) and peptide nucleic acids (PNAs), which offer increased stability, half-life and binding affinity to targets.

In the past, it was hard to introduce oligo therapeutics anywhere other than the liver without direct injections. This greatly reduced the types of diseases that these drugs could effectively treat. To date, only sterile injectable products are approved—but oral and inhaled oligo delivery approaches are being pursued as well. And, as clinically

effective solutions in treating diseases occurring in non-hepatic tissues are found, many new forms of oligo drugs will continue to reach the market.

REGULATORY BODIES ARE TAKING NOTE

The COVID-19 pandemic triggered the rapid development and widespread use of mRNA vaccines. This has accelerated the research, development, and regulatory acceptance of all RNA products by many years—maybe even decades. In August 2021, Pfizer experienced a huge win as their mRNA vaccine received full approval from the FDA. Time will tell if changes to the regulatory landscape based on this success story for COVID-19 vaccines will extend to new genetic-based technologies such as oligonucleotides.

COMMERCIAL MANUFACTURING APPROACHES

Given these market forces, how should companies be approaching scale-up and commercialization? This largely depends on how the molecules are synthesized. While mRNA is a biological molecule that is built or replicated using biological or enzymatic approaches, oligonucleotides call for different design considerations due to the flammable solvents and chemical reactions involved in their production.

20 years ago a single gram of amidites cost

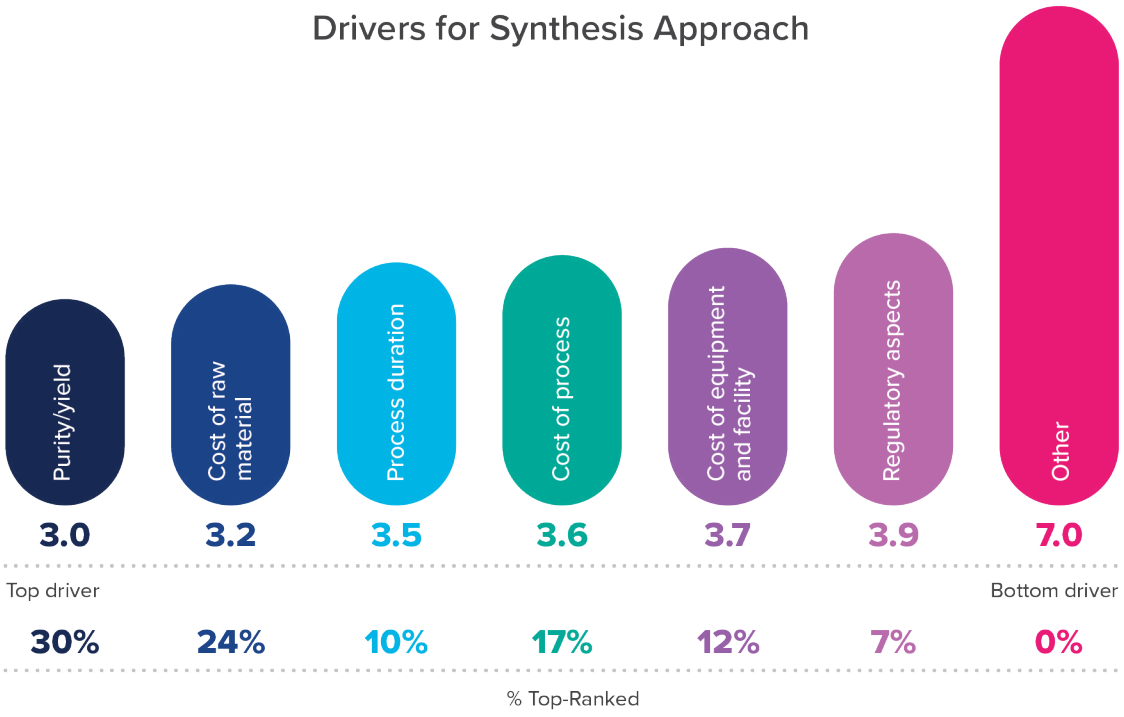
$10,000

Historically, the main driver in choosing an oligonucleotide synthesis approach was the cost of raw materials and the purity and yield of products. For example, just 20 years ago, a single gram of amidites (a key raw material for oligo chains) cost roughly $10,000. Since then, interest has driven supply volume up and brought prices down considerably. As the price of key raw materials continues to drop, other manufacturing decision drivers have come into view, including throughput and cost of equipment and facilities (Figure 14).

Oligonucleotides are further dependent on chemical supplies (e.g., large quantities of solvents like ACN), which puts the industry at risk for supply chain issues. As the industry scales up, this may create strain—despite the fact that these molecules make up a tiny fraction of the chemical market. Therefore, robust warehousing and supply chain management is important. Process improvements that increase production yields and reduce waste will also have a higher impact on oligo facilities than in some other therapeutic areas. Management of these areas of the business, such as onsite recycling of ACN, will gain attention as the industry matures and more large-scale therapies hit the market. At the same time, further exploration into green chemistries may eventually pivot the industry away from classical solid-phase synthesis.

FIGURE 14

What are the primary drivers of your chosen synthesis approach? 1=Top driver, 7=Bottom driver



Source: CRB

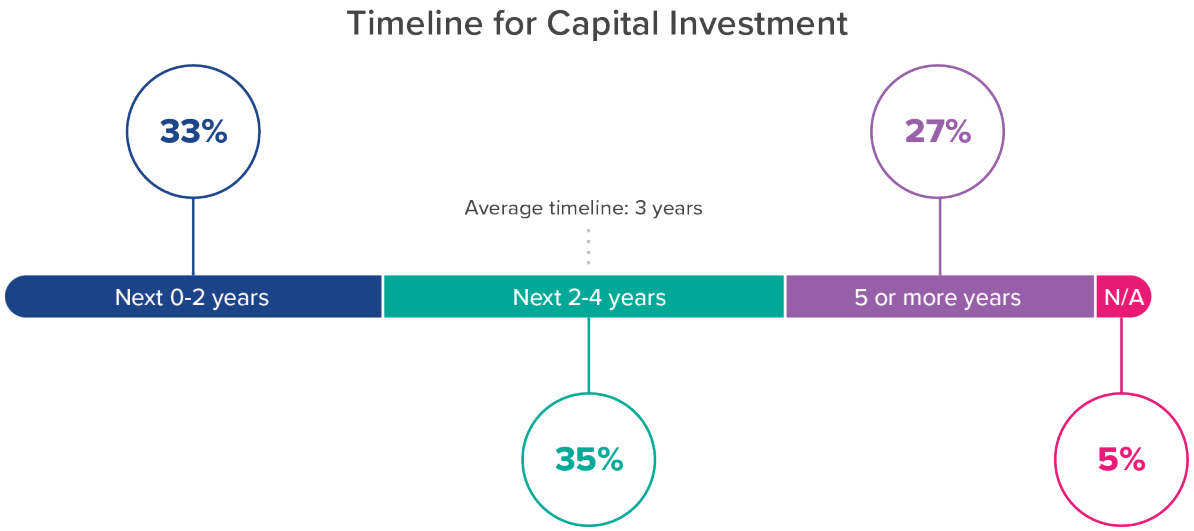
USE OF CMOS AND CAPITAL INVESTMENT TIMELINE

Currently, there are only a handful of large-scale oligonucleotide contract manufacturers in the world—and feedback from our clients indicates they have limited capacity to take on additional contracts in the foreseeable future. This suggests that CDMO suppliers could be lagging behind the surge in oligonucleotide drug development company demands for large-scale clinical and interim launch capacity. Even as some CDMOs continue to build facilities and increase available capacity, the delay to gain a production window may improve the business case for newcomers to the oligo space to undertake capital projects and develop their own manufacturing capacity. Self-manufacture can also provide a measure of independence for companies that utilize oligonucleotides as the basis for their therapeutic drug programs and allow them to protect their IP.

This is borne out by the survey data as two-thirds (68%) of respondents are planning to invest capital in in-house oligonucleotide therapeutics manufacturing within the next four years (Figure 15). This group is well represented within large pharma companies (82%), start-ups (61%), and CDMOs (80%), indicating to us that the time for investment is at hand (Figures 16-18). This near-term focus on investment further signals the growing momentum of the industry as more oligonucleotide drugs move towards approval.

FIGURE 15

If you are considering at least some in-house manufacturing, what is your timeline for capital investment?



Source: CRB

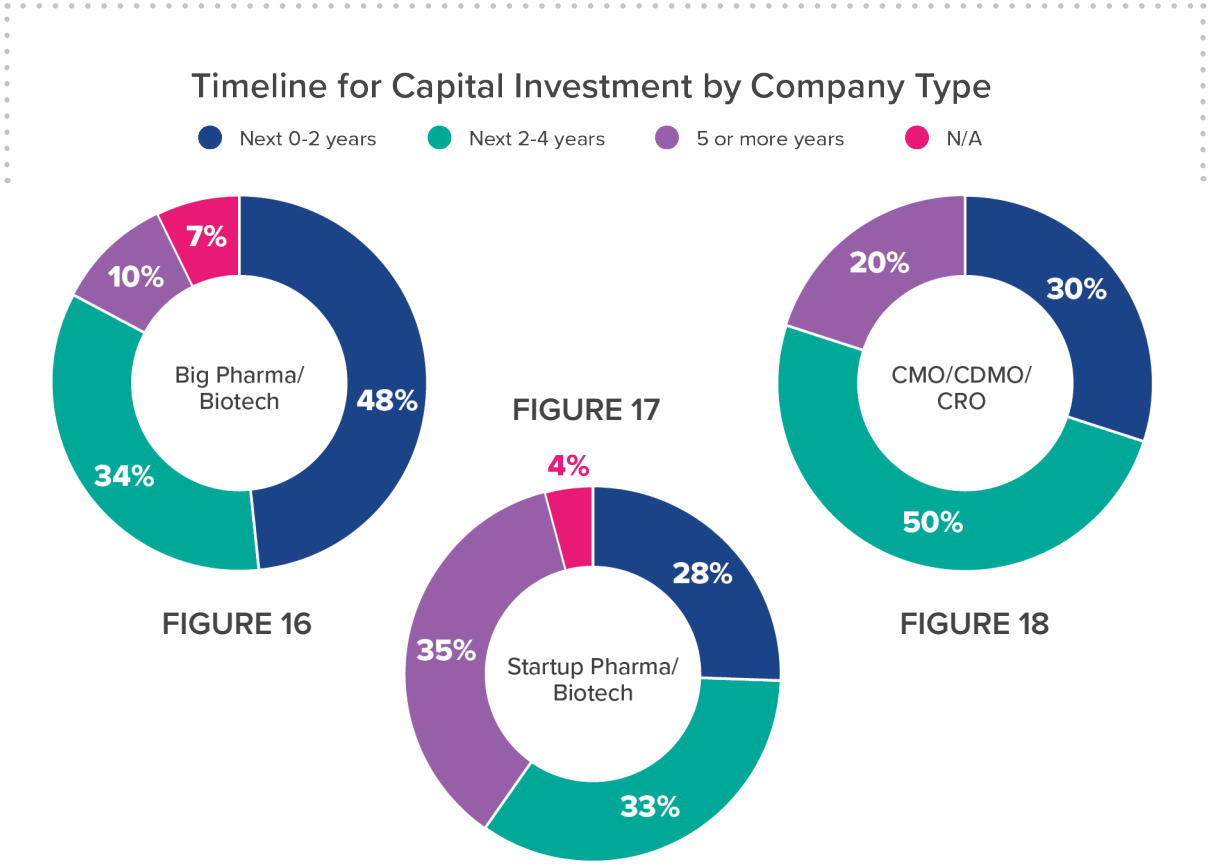


FIGURE 16

FIGURE 17

FIGURE 18

Conclusion

The scientific progress of the last 20+ years has yielded an incredible understanding of the genetic causes of many diseases, leading to new approaches to how we can treat those diseases. Oligonucleotides are poised to rise to the challenges of many previously intractable diseases while also improving on current treatments for many common disorders. The steady surge in investment in oligonucleotide pipelines and facilities has become harder to ignore and gives clear indication of the promise of this technology for years to come.

RNA Technology:
Combating disease with more versatile and faster-to-develop molecules

By David Estapé, Ken Jacobson, Can Aktar, and Jake Adams




Before there was COVID-19 there were mRNA companies, but they weren't focused on contagious disease vaccines. They were focused on loftier indications where no current treatments exist. The idea of an mRNA vaccine had been explored in academia and even pursued for Zika virus, SARS, and H1N1 flu, but those epidemics subsided before the vaccine was developed and momentum for commercial development was lost.

Then along came SARS-CoV-2. The severity and scope of the pandemic quickly made it clear that even drastic social controls weren't going to be sufficient and a combination of vaccines and therapeutics was going to be needed. As the race to develop vaccines began, there was much speculation about what a 'warp speed' timeline could look like. As updates began to roll in, mRNA vaccines emerged as the solution most likely to fit the bill. Companies could leverage all of their previous R&D to speed development, as well as accelerate progress due to the ease of recruiting more than 40,000 people for clinical trials. As a not-yet-commercialized platform, questions remained about the ultimate efficacy of an mRNA vaccine, but skeptics were pleasantly surprised as the trial data approached 95% efficacy.

mRNA vaccine trial efficacy approached

95%

With that incredible efficacy data came a shift in the industry's attitude toward RNA technology. Two years ago, RNA was largely regarded as a theoretical "good idea" in the race to discover more effective therapies. RNA has shown that its time is now,

and is set to irrevocably disrupt not only the industry's approach to vaccines but the way we think about treating a range of conditions, including autoimmune diseases, high cholesterol, cancer, and rare diseases. That's why nearly every large pharma company has quickly moved to incorporate RNA technology-based products and manufacturing capacity over the last year.

RNA technology refers to much more than mRNA vaccines. Oligonucleotides—short strands of chemically synthesized RNA, including small-interfering RNA (siRNA) and antisense oligos (ASOs)—have been racking up clinical approvals in obscure indications (e.g., hATTR amyloidosis) and crowded spaces (e.g., PCKS9-related high cholesterol). Headline-grabbing CRISPR gene-editing systems rely on single guide RNA (sgRNA) to locate the genes to be modified. Even mRNA itself has found new momentum toward target indications including cancer and autoimmune diseases.

While the recent success and headlines haven't solved all the challenges of RNA-based therapies, including the need for a cold supply chain, short biologic half-life, and delivery to specific tissues, the future appears bright for these new kids on the block.

"Capacity to produce mRNA went from clinical levels to supplying the world with mRNA vaccines in a matter of months, a feat that represents one of the greatest accomplishments of the biopharma industry to date. It's no longer 'if' RNA technology will be the next biopharma wave, it's 'what' will RNA technology cure next."

RNA-BASED THERAPIES ARE BEING USED FOR A WIDE RANGE OF DISEASES

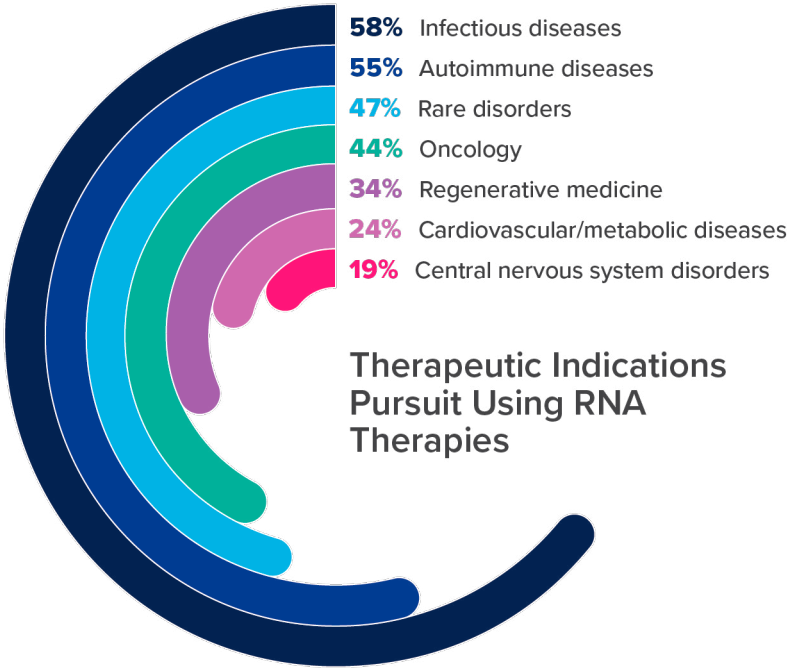
Almost all respondents believe that RNA-based therapies will have disruptive potential for drug manufacturing (Figure 19.1) while the average company intends to pursue RNA-based therapeutics for multiple indications (Figure 19.2: average respondent selected 2.5 indications). This highlights an aspect that has helped increase interest in RNA technology: these platforms have wide applicability and there is minimal additional capital investment required when pursuing multiple RNA molecules within the same technology family. The changeover in a facility to switch from mRNA infectious disease vaccines to mRNA that cures an autoimmune disease may be as simple as a thorough cleaning, as raw materials, equipment, and process spaces would be largely unchanged. A facility that can exist through multiple product life cycles without significant capital expenditure or downtime makes for a better investment than predecessor biopharma therapies.

The data also paints an interesting picture of the types of indications being pursued (Figure 19.2). While no single entry is surprising, as companies are quick to roll

out marketing with any pre-clinical success, collectively the industry seems to be targeting indications that include both orphan and currently served indications. On the surface we would expect focus on a developing technology to be on conditions for which no, or limited, therapies currently exist. In the case of orphan diseases, securing regulatory fast-track commitments and first-line treatment designations—and, therefore, most of the market share—is a more commercially attractive approach. While orphan diseases do not represent a large patient population, these treatments only need to account for a small portion of a facility's annual production to remain viable and can therefore justify investment in a facility that will support launch/manufacturing capacity for their pipeline.

FIGURE 19.1

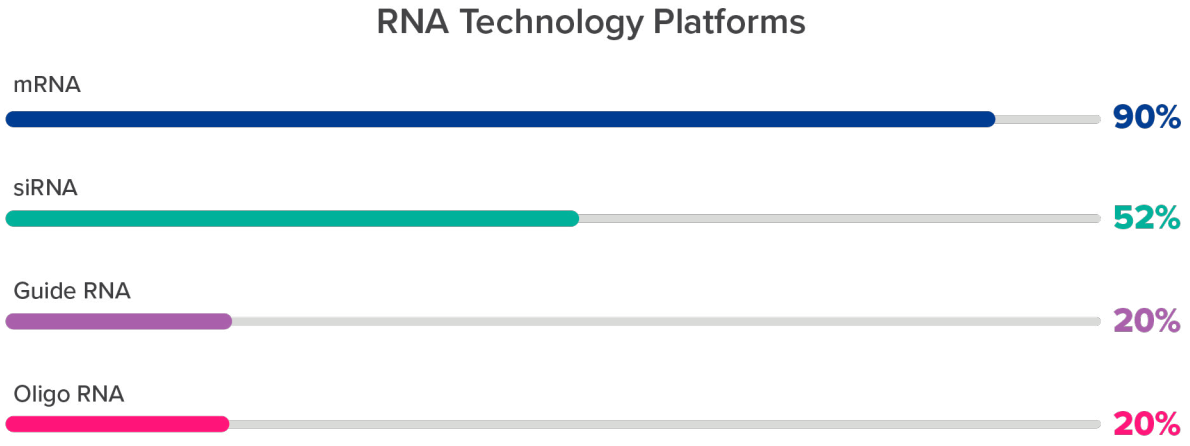
What therapeutic indications does your company intend to pursue using RNA-based therapies?



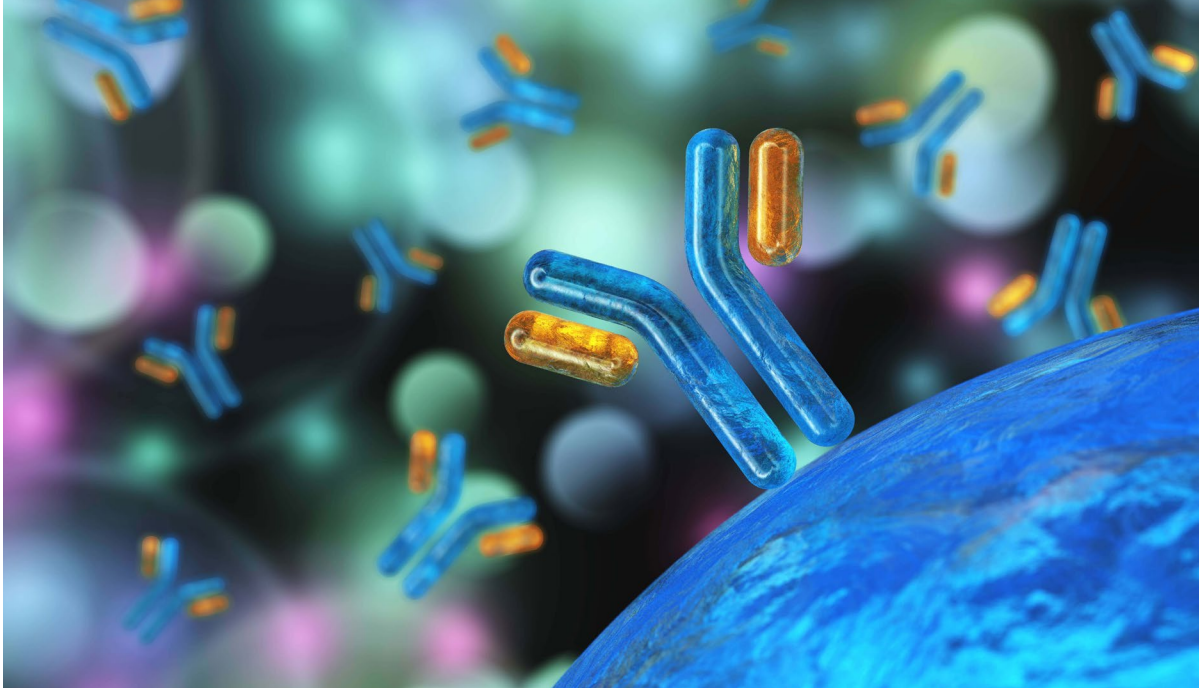
Source: CRB

FIGURE 19.2

What platforms of RNA technology and products is your company pursuing? (Select all that apply)



Source: CRB



Conversely, autoimmune diseases and oncology are high-profile and crowded therapeutic indications. Multiple immunotherapy monoclonal antibodies (mAb), such as Imfinzi, have revolutionized treatment options for certain cancers. There are several existing mAb treatments for autoimmune diseases, including blockbusters like Enbrel, Humira, and Remicade for rheumatoid arthritis. No doubt there is room to improve tolerability and therapeutic benefit of some of these treatments, but the fact that 55% and 44% of companies pursuing RNA-based therapeutics are targeting autoimmune disorders and oncology, respectively, suggests they believe these RNA platforms have the potential to improve upon existing therapies by offering a more effective, tolerable, and economical treatment. The first glimpse at RNA therapeutics vs. incumbents looks to be PCKS9-caused high cholesterol where siRNAs (Leqvio) and mAbs (Repatha) look to supplant statins.

The preference for pursuing RNA-based therapies for infectious diseases makes sense given the success of mRNA vaccines for the treatment of COVID-19 and the influx of both private and public funding into the industry. That success has flu vaccine manufacturers asking whether they should be replacing their cell-based production with mRNA. The obvious advantages—rapid production, ease of rapidly shifting to match a new virus strain or variant each year and, even, within a flu season, smaller dose required, and lower cost of goods—are disruptive drivers for uptake of this technology.

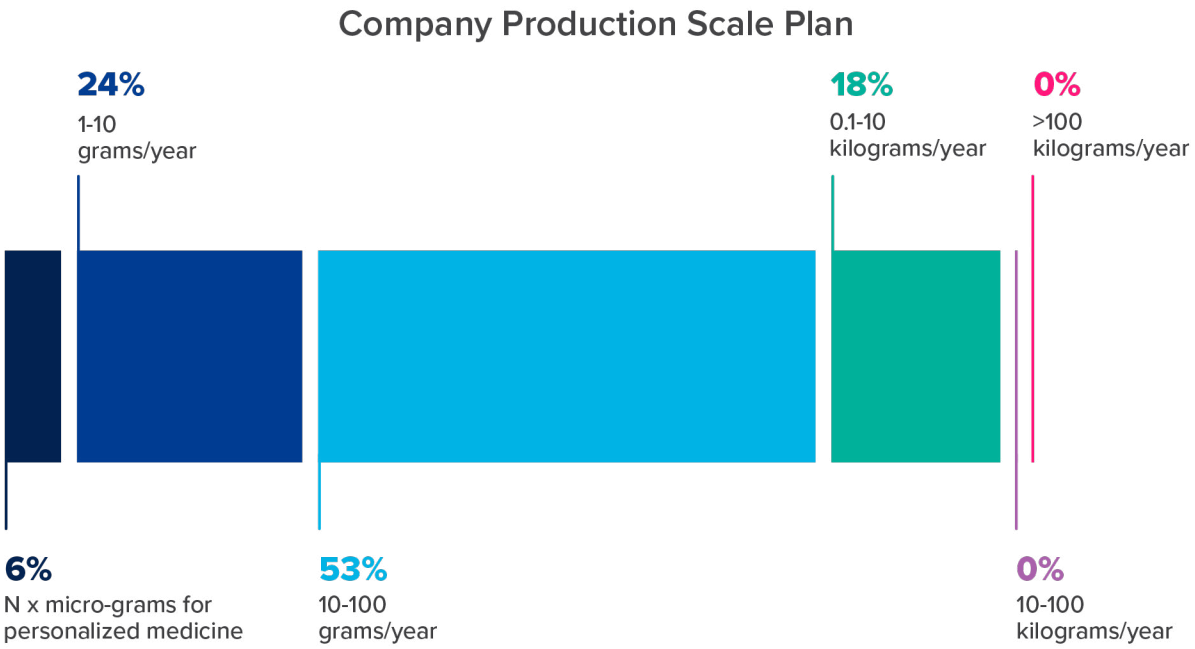
It is clear that respondents believe this technology could improve tolerability and therapeutic benefit for some indications, even those already crowded with effective drug products. Another salient takeaway from this data is that a facility designed to use mRNA for regenerative medicine or to produce a vaccine for an infectious disease could also be used to make treatments for a rare disorder or an autoimmune disease. The possibilities for internal synergy are strong, which is good news from a business strategy standpoint and from the point of view of patients waiting for a new generation of effective, or even curative, treatments.

COMPANIES INTEND TO PRODUCE MODEST AMOUNTS OF RNA PRODUCTS

With a small sample size (n=17), more than half (53%) said their company is planning to produce 10–100 g/year of RNA products (Figure 20). This is a modest amount compared to the roughly ten kilograms of mRNA needed yearly by the makers of COVID-19 vaccines. It confirms the impression that, despite dominating headlines, RNA therapy is still in its adolescence. While a significant number of therapies may never require even a single kilogram per year to serve the entire patient population, even 10 g/year represents a shift beyond the discovery phase, which only requires microgram to milligram quantities, and a move into early clinical trials.

FIGURE 20

What production scale is your company planning for?

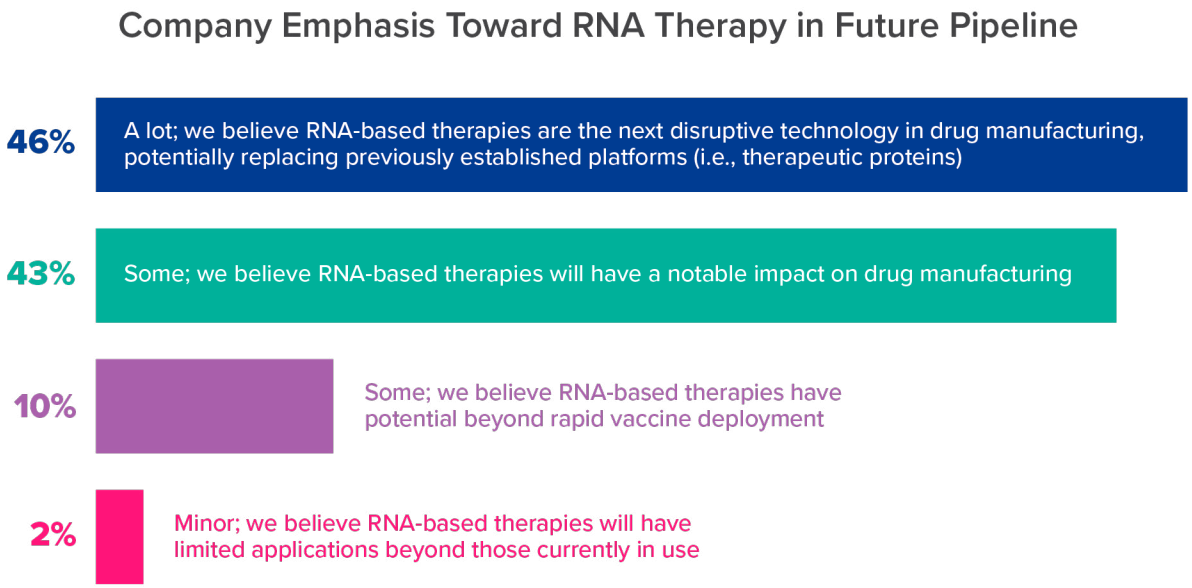


Source: CRB

CURRENT USERS ARE BULLISH ABOUT RNA'S POTENTIAL

FIGURE 21.1

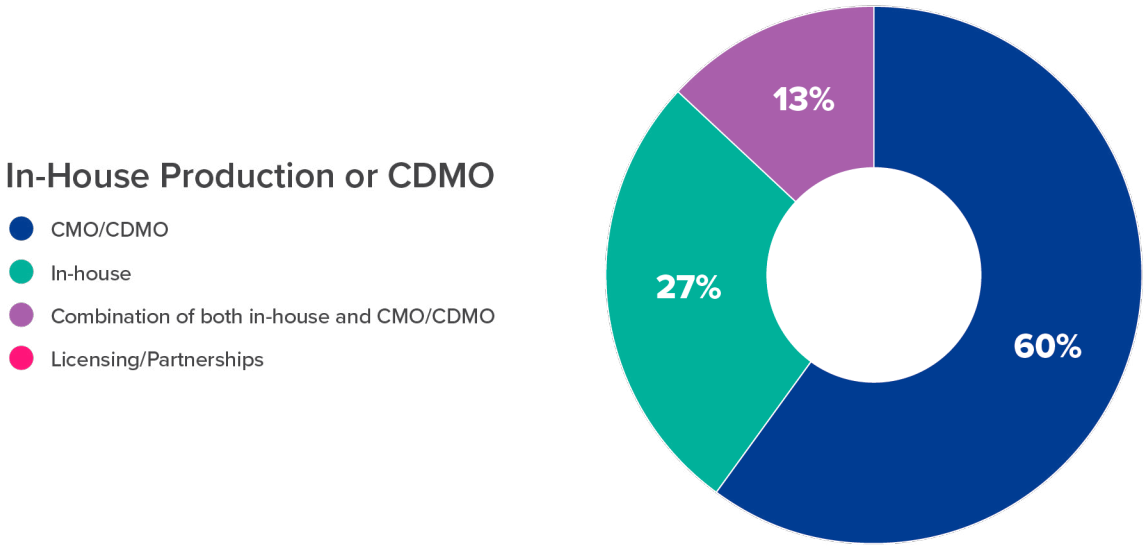
How much emphasis is your company putting toward RNA-based therapies becoming a major emerging portion of your future pipeline?



Source: CRB

FIGURE 21.2

Do you intend in-house production or using a CDMO?



Source: CRB

Of respondents who embrace RNA technology, more than 98% will be putting some or a lot of emphasis on RNA-based therapies becoming a major part of their future pipeline. Respondents believe these platforms will disrupt drug manufacturing by potentially replacing existing manufacturing platforms and by finding applications beyond vaccine production (Figure 21.1).

Given that, for now, the quantities needed of most RNA products are small, there is a logical preference to outsource production. This is reflected in the fact that most respondents (60%) intend to enlist a CMO/CDMO to produce their RNA products (Figure 21.2). However, the rising popularity of RNA-based therapeutics, combined with the limited capacity of CMO production space, especially for RNA-based technology, means a company might have to wait up to two years before delivery of its first batch. This is a trend that has driven up prices. This move is mirrored in the oligo sector, where 45% plan to pursue in-house manufacturing. Among those considering in-house production, the average timeline for capital investment is three years.

60%

of respondents intend to enlist a CMO/CDMO to produce their RNA products

Traditional biopharma platforms left companies two choices when faced with contract manufacturing capacity shortages: wait for contract manufacturing capacity to get out ahead of demand or plunge into a capital project where right-sizing future capacity needs and current funding were nearly impossible. With RNA therapeutics, facilities that are both cost-effective on day one and allow for cost-effective best-case growth in demand are possible.

THE RISE OF MODULAR AND DEPLOYABLE FACILITIES

The facility-type disruption caused by RNA-based technology is partly due to its detachment from large-batch cell culture; there is simply no need for a huge facility with huge bioreactors and the associated downstream equipment. Instead, manufacturers can produce their required amounts in modular, rapidly built, local facilities.

Talk about disruption and economy of scale. Doubling RNA manufacturing facility capacity isn't a full redo; it's copy and paste.

Once the drug manufacturing process is understood, it can be organized into shipping-crate-sized modules, manufactured in state-of-the-art factories, and shipped anywhere in the world. On site, these process modules can be placed inside a simple office and warehouse building shell for a 'box-in-a-box' facility. When more capacity

is needed, another module can be copied and then pasted next to existing ones with minimal interruption. With sufficient planning, the process modules can even be combined with office and warehouse modules for a building that comes together as easily as Lego®.

In fact, many jurisdictions far away from biotech hotspots are looking to build mRNA facilities for domestic vaccine production. And, while oligo platforms require a different type of facility, the same is true for them. This is possible because RNA production batches tend to be smaller and future product flexibility doesn't require large amounts of square footage—say goodbye to 20,000-L stainless steel cell culture bioreactors producing thousands of kilograms of drug product per year. Instead, an RNA plant, built for $50 million, could manufacture enough product, or even multiple products, for a region—or an entire country.

Unlike other pharmaceuticals, these unique manufacturing attributes mean that companies can make RNA drugs close to the patients who need them, which simplifies shipping logistics and improves access. The efficiency and commodity of scale of this model have already been proven. It is now just a matter of stamping out a copy to deploy it, even in areas where there is no other current pharmaceutical manufacturing going on.

SPEED-TO-MARKET AND LOWER COST OF GOODS TOP ADVANTAGES OF RNA TECHNOLOGY

When potential advantages of RNA-based platforms over traditional biopharma technology were ranked, speed-to-market and cost of goods came out on top (Figure 22).

While the raw materials to fabricate RNA—modified bases, specialized enzymes, plasmid culturing, and high-quality DNA—have a high cost per gram, cost of goods is ultimately lower because the need is for such small amounts. Also, when compared to making monoclonal antibodies, which require large amounts of water, buffer, CIP, steam, and energy, the RNA facility footprint and equipment are of a much smaller scale and cost.

The RNA facility footprint and equipment are of much

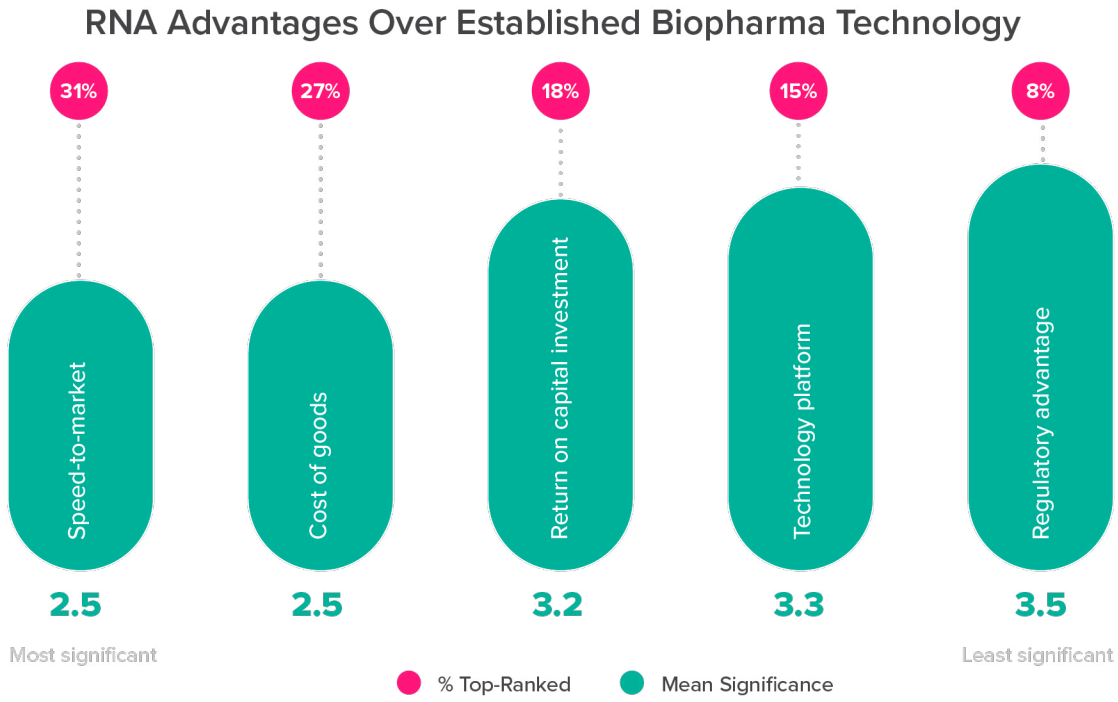
smaller scale and cost

compared to making monoclonal antibodies

While only 8% ranked regulatory advantages at the top of the list of RNA technology advantages, we believe these will turn out to be significant. The proven safety of the mRNA COVID-19 vaccines has paved the way for the therapeutics to come, no doubt shortening their timeline to approval. There could also be a case made that modifications to the mRNA in a vaccine—for example, to address viral variants—could require shorter safety studies and more rapid approval, since scientifically, product safety has little to do with the virus itself and more to do with spike protein.

FIGURE 22

What are the most significant advantages of RNA technology?
1=Most significant, 5=Least significant



Source: CRB

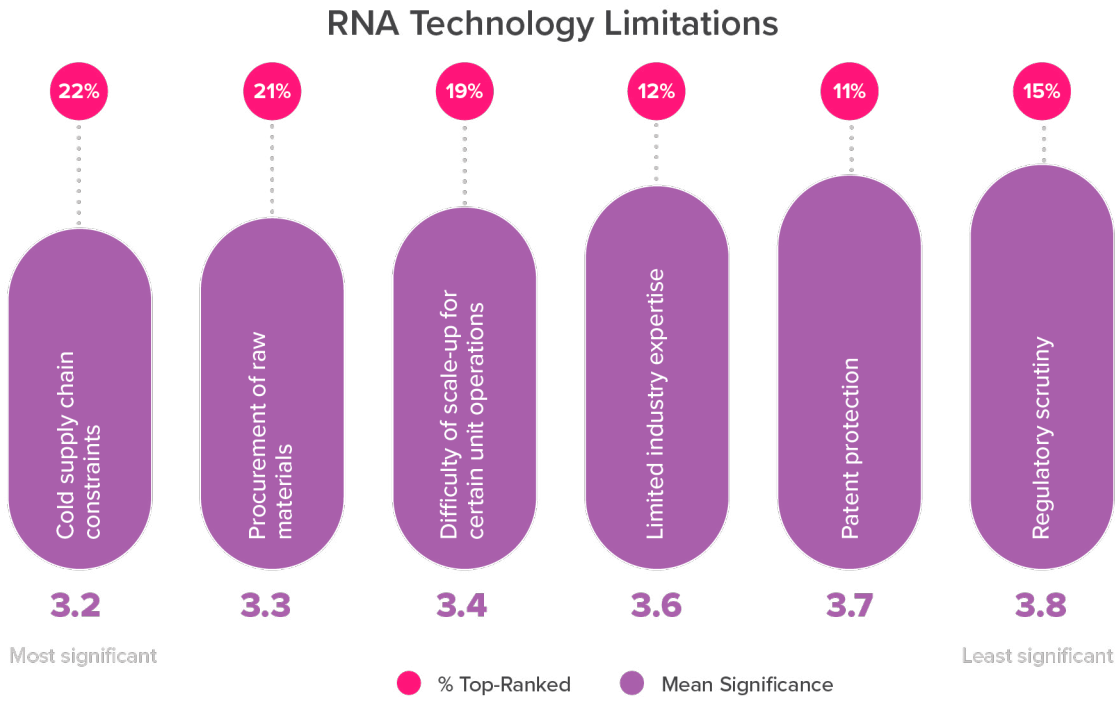
STILL, THERE ARE CHALLENGES TO OVERCOME

Even with its disruptive potential and advantages over conventional biopharma manufacturing, respondents noted the limitations of RNA technology, including the need for a cold supply chain, procurement of raw materials, and difficulty scaling up some unit operations (Figure 23).

While the top-ranked concern among respondents was cold supply chain constraints, this seems to be melting away as product stability is more thoroughly studied. The stability of mRNA is essential to the success of vaccines and, to ensure this, the COVID-19 vaccines were stored at ultra-cold temperatures during testing and launch. We now know they can be safely stored long-term in a -20°C conventional freezer and ongoing studies will soon uncover more ways to improve the drug's stability.

FIGURE 23

What are the most significant limitations of RNA technology?
1=Most significant, 6=Least significant



Source: CRB

CONCERN ABOUT POST-PANDEMIC OVERSUPPLY OF MANUFACTURING CAPACITY MAY BE MISGUIDED

Of respondents using or intending to use RNA technology, well over half (58%) said they were concerned about the potential for too much capacity once the pandemic ends. This is surprising, given the backlog in facilities currently making mRNA for vaccines. Perhaps there is some apprehension that developments of therapies for other indications will lag behind as we reach the end of this pandemic. However, with the Delta variant spreading rapidly, the need for COVID-19 vaccines is unlikely to ramp down as quickly as we had hoped. Also, we are optimistic that other mRNA products are going to reach late-phase clinical trials and that commercial scale-up will be well underway before companies are finished making COVID-19 vaccines—if they are ever finished.

Despite this concern, the advantage of RNA facilities is that they have a smaller footprint, lower capital costs, and can switch what they're making from, say, mRNA for COVID-19 vaccines, to mRNA for flu vaccines or other biologics. Thus, any excess capacity could be transitioned to make products for another indication. RNA facilities designed for oligo technology platforms have similar flexibility.

If this sounds optimistic, consider the history of monoclonal antibody (mAb) manufacturing. Just as some of today's companies are concerned about oversupply in mRNA production, early mAb manufacturers wondered if their facilities, which came with a huge infrastructure bill, would pay off. We know what happened next: new mAb therapies emerged in rapid succession over many years, and industry leaders went from worrying about having too much capacity to building huge base facilities with multiple 20,000-L bioreactors in a race to meet ongoing demand. mRNA manufacturers will likely experience the same kind of upwards trajectory, which, interestingly, could lead to overcapacity challenges for some of those mAb manufacturers, whose products may soon be displaced by better, more effective mRNA therapies.

As a result of real-time analytics assisting us in managing and taking appropriate actions, the situation appears to be under control.

New therapies and improvements on current therapies are on the horizon

Quicker development time, smaller facilities with streamlined processes, and a promise of safety, versatility, and increased speed-to-market; these are the reasons RNA technology has the potential to replace current therapies for existing indications. We expect that over the next decade, these versatile platforms will become faster to develop, approve, and adopt than other biologics and will lead to more of the kind of life-saving therapeutics we've seen arise during the pandemic.

Operations

SECTION TWO

Predicting the Future:

The industry embraces digitalization and Pharma 4.0™

By Yvonne Duckworth, Niranjan Kulkarni, and Matt Edwards

Even before the pandemic, it was hard to keep up with the pace of change in the pharmaceutical industry. Then along came COVID-19, and that pace accelerated. We had to rethink our manufacturing systems, optimize processes, and learn to function remotely. As with so many other aspects of our industry, the pandemic has sped up the adoption of digital tools, which is a large part of Pharma 4.0™ and has enabled new efficiencies like remote collaboration on design and construction and factory acceptance testing.

Pharma 4.0™ is about bringing digitalization to pharmaceutical manufacturing

Pharma 4.0™—an incorporation of the Industry 4.0 operating model into our industry—is about bringing digitalization to pharmaceutical manufacturing through such technologies as artificial intelligence, data analytics, robotics, biometrics, and cloud computing. Old ways of doing things—paper batch records and SOPs, automation silos—are giving way to connected plants with high levels of automation, real-time predictive analytics, and, at the pinnacle, autonomous manufacturing facilities with plug-and-play processes. Companies that embrace Pharma 4.0™ are able to harmonize the flow of data from R&D through manufacturing and distribution, enhance cybersecurity, and improve their quality and regulatory compliance.

But getting to a fully digitalized and connected facility can be challenging. Biopharma, in fact, is lagging behind other industries in implementing digital technologies, in part because of the more rigorous regulatory environment in which it operates. We asked those in the industry to share their opinions on Pharma 4.0™ and to tell us where they're headed, how quickly, and what's holding them back.

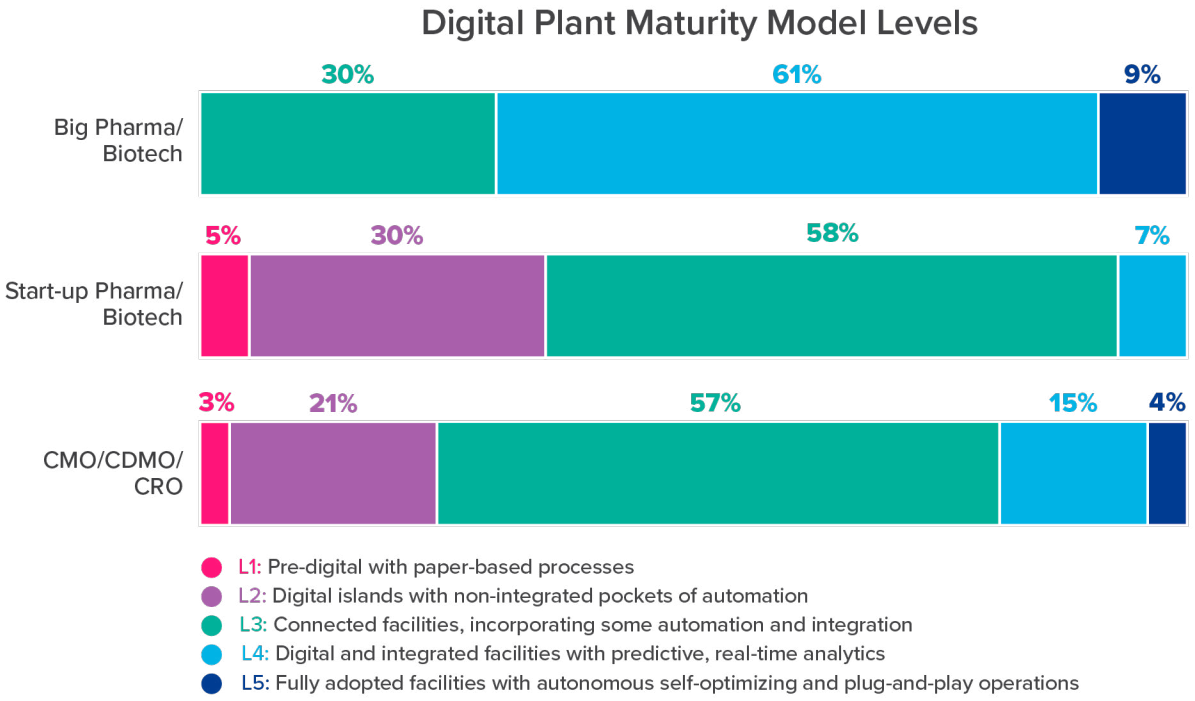
COMPANIES WANT TO REACH THE NEXT DIGITAL PLANT MATURITY LEVEL, MOST AIMING FOR LEVEL 4

The Digital Plant Maturity Model (DPMM) categorizes plants based on their level of digitalization, automation, and data integration between teams. Predigital plants (Level 1) use manual and paper-based processes, while adaptive plants (Level 5) are fully autonomous and self-optimizing.

Slightly more than half of all respondents said their company is at DPMM Level 3 (Figure 24). This aligns with what we see from our own clients over the past three years, most of whom are at either Level 2 or 3. However, large biopharma companies skew toward Level 4 (61%), while significantly fewer start-ups and CMOs have achieved this level of digitalization.

FIGURE 24

What DPMM level most accurately describes your company?



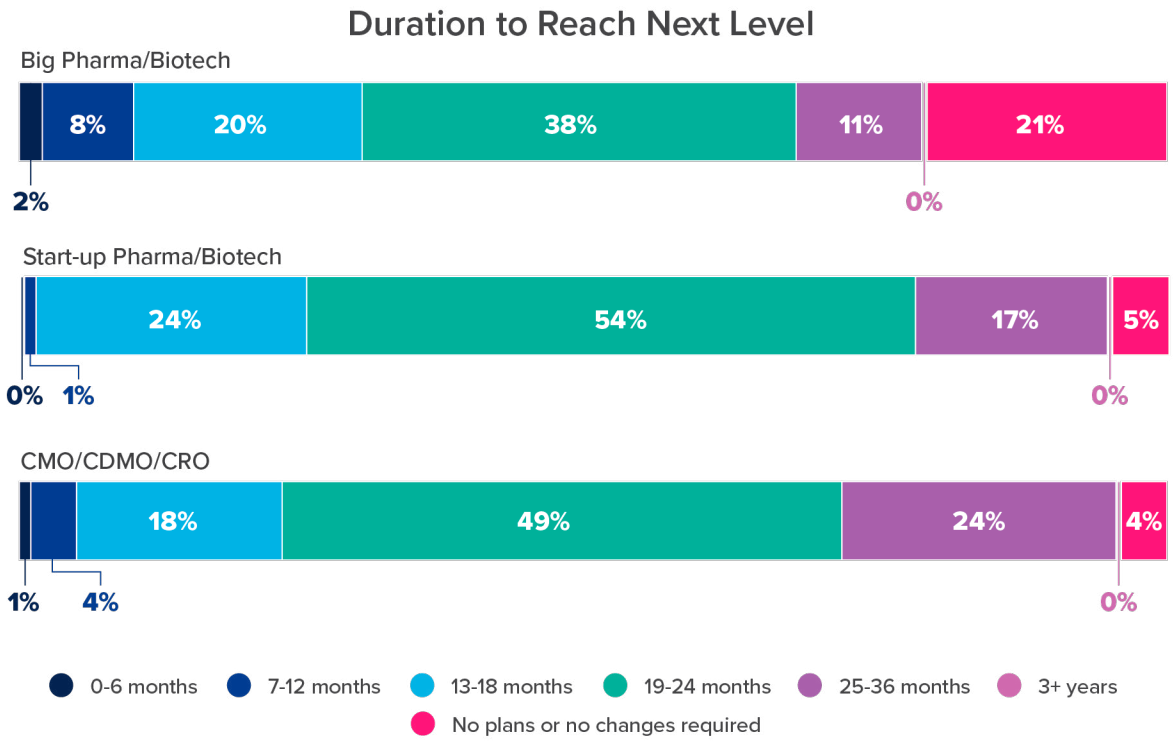
Source: CRB

When asked to what level they aspire to reach in the near-term, almost all are aiming for their next highest DPMM level. Three-quarters of all respondents estimate they will reach the next DPMM level within two years (Figure 25).

One of the most valuable benefits of achieving Level 4 is the ability to use predictive analytics, such as a vibration monitoring system that knows when a motor is likely to fail. This is a key ask of every client who is seeking to improve their company's digital maturity, because anticipating problems before they happen can dramatically reduce downtime.

FIGURE 25

How long will it take your company to reach that DPMM level?



Source: CRB

CHALLENGES TO DIGITAL EVOLUTION

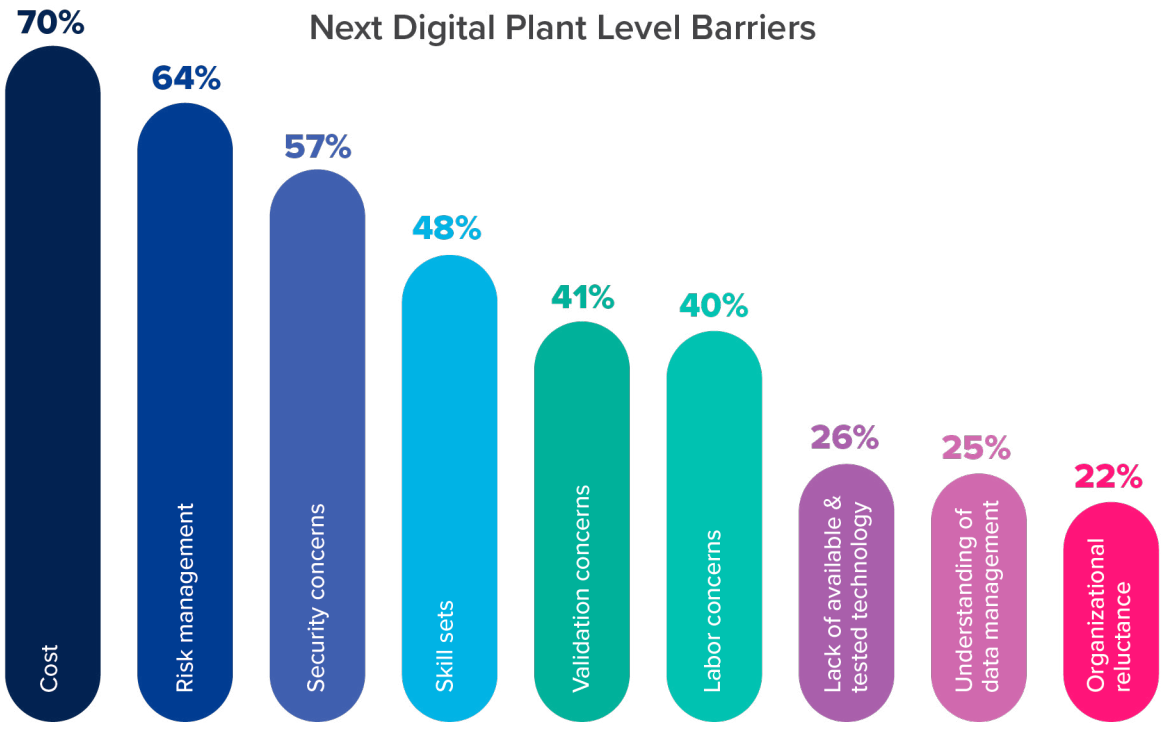
When we asked respondents to identify the impediments they face in reaching the next DPMM level, they ranked cost, risk management, security concerns, and skill sets at the top of their lists (Figure 26). The upfront costs of digitalizing a new or existing plant may be great, but the financial rewards of reduced downtime, fewer lost batches, and less human error will likely offset that initial outlay.

There is overlap between managing risks for such things as manufacturing operations, unscheduled downtime, and safety, and mitigating security concerns to protect data and intellectual property. For example, one client wanted to use advanced analytics to predict the flu vaccine. While this was a good idea, there was some risk associated with securing the intellectual property data.

Almost half of our respondents mentioned skill sets as a significant barrier to reaching the next digitalization level. It is important to anticipate how improving your facility's digital maturity level will impact your workforce. The number and type of employees needed will definitely change. Some skill sets will become obsolete with automation or the addition of robotics, while allowing a wide range of functions to be performed faster and cheaper. On the other hand, the reams of additional data collected will need to be analyzed by data scientists. We have seen large pharmaceutical companies hiring experienced data analysts from outside the industry (e.g., from Microsoft). These are interesting strategic hires, bringing in experts who lack a background in the pharmaceutical industry but have the digitalization experience to see things through a different lens.

FIGURE 26

What are your barriers to reaching the next DPMM level?



Source: CRB

We have found that the best way to address these hurdles is to develop a phased or scalable approach, implementing one digital tool at a time, then adding more as needed. Putting in the infrastructure to accommodate these sequential additions over a few years allows companies to spread out implementation, thus reducing stresses in both cost, culture, and processes. It is important to ensure that your workforce is behind this maturation process, from the boardroom to the plant floor, because it is going to change how things are done. There may be workers concerned about losing their jobs or merely intimidated by newer technologies.

While only one-quarter believed an understanding of data management was a barrier, we feel this is a much more significant challenge. Understanding operational data is one thing, but to ascend through the DPMM levels toward the ideal state in which all the data—from facilities, operations, maintenance, BMS information, design, and construction—is available, shared, and understood across functions is a challenging issue that is still fairly messy. Currently, there are no international standards or guidelines that dictate the interoperability of data or structuring data between tools.

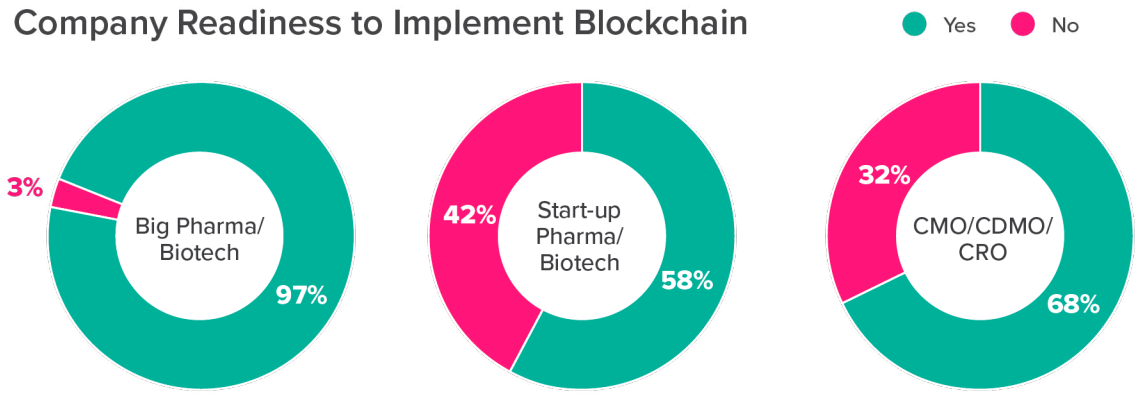
COMPANIES SAY THEY'RE READY TO USE BLOCKCHAIN; NOT SO FAST

Blockchain is seen as an important aspect of securing supply chain information in many industries, most notably allowing banks to track and trace the flow of financial information. There is a desire and willingness to use blockchain for pharmaceutical manufacturing, particularly for the supply chain. (Once the process is inside the four walls of a facility, there are different ways of tracking that won't increase the computational power needed.)

Surprisingly, two-thirds of respondents said their companies are ready to implement blockchain to secure their supply chains, including 97% among larger companies (Figure 27). We believe this is optimistic; honestly, our industry is not at all ready.

FIGURE 27

Is your company ready to implement blockchain to strengthen security of your supply chain?



Source: CRB

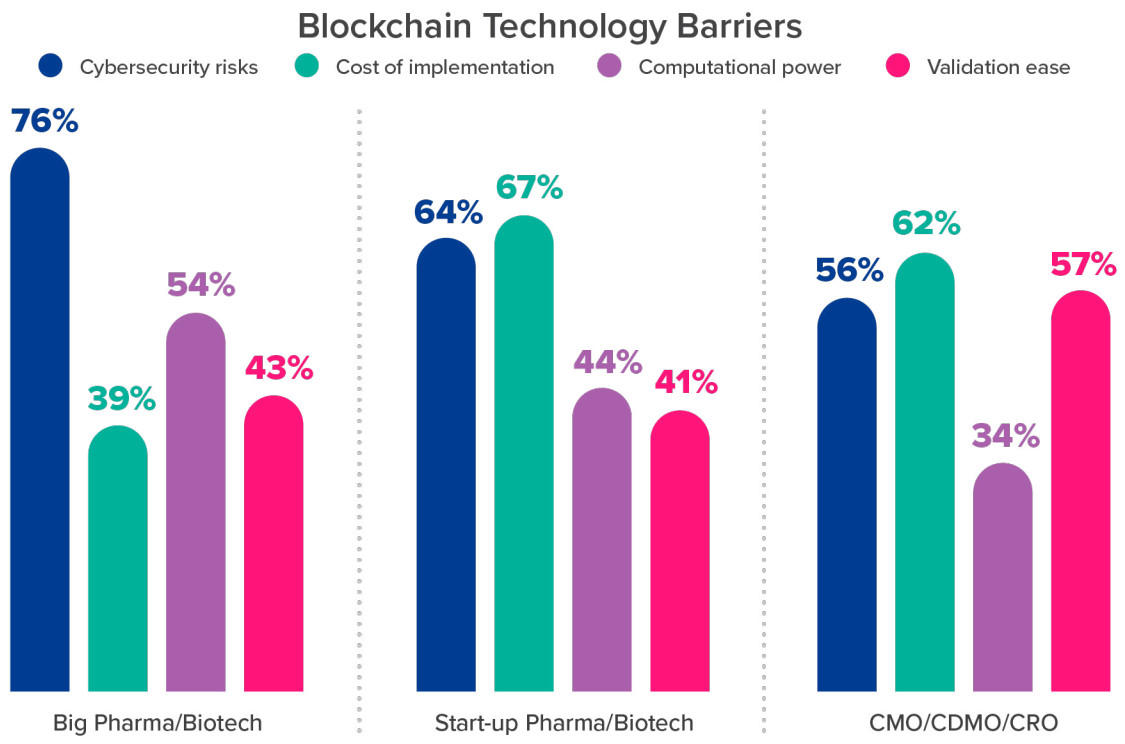
The reasons that we believe this is wishful thinking are highlighted by the list of barriers to blockchain implementation that respondents identify as significant (Figure 28). While cybersecurity risks and implementation costs top that list, they aren't the biggest barriers in our experience. Cost to implement is a minor factor; if you can implement an Oracle system, the cost is not going to be too onerous. Obviously having a secure network and infrastructure is essential, but this shouldn't be a barrier when working with an experienced vendor.

Instead, what is holding back widespread adoption of blockchain is a lack of computational power, identified by less than half of respondents and only one-third of CMOs. Consider the poster child of the blockchain, Bitcoin, which is not significantly impacted by cybersecurity risk. Instead, the price continues to rise because there is not enough computational power to mine more Bitcoins.

Another barrier, not listed here, is a lack of understanding of what needs to be encrypted on the blockchain. Will you add quality data or just the supply chain data? To implement blockchain, you first need to understand it, and we believe much more education is needed before the pharmaceutical industry reaches that point.

FIGURE 28

What are your barriers to implementing blockchain?



Source: CRB

AI HAS SIGNIFICANT BARRIERS

Many biopharma companies are using artificial intelligence (AI) to optimize manufacturing by collecting and parsing production information. Our clients are using AI for predictive analytics and predictive maintenance to anticipate failures and to minimize downtime. Real-time analysis of feedback loops allows them to adjust conditions to improve manufacturing. This fits well with the continued interest in quality by design, and a good AI system allows quality testing using near real-time, in-line quality control.

Among all respondents, the top concerns for implementing AI are cost, cybersecurity risks, and skilled labor (Figure 29.1), in keeping with our experience. In particular, skilled data analysts and other labor can be in short supply and this impedes implementation.

Respondents intend to use AI for quality testing (71%), to improve material planning (59%), for predictive analytics (53%), and to improve efficiency (52%) (Figure 29.3).

ELECTRONIC BATCH RECORDS

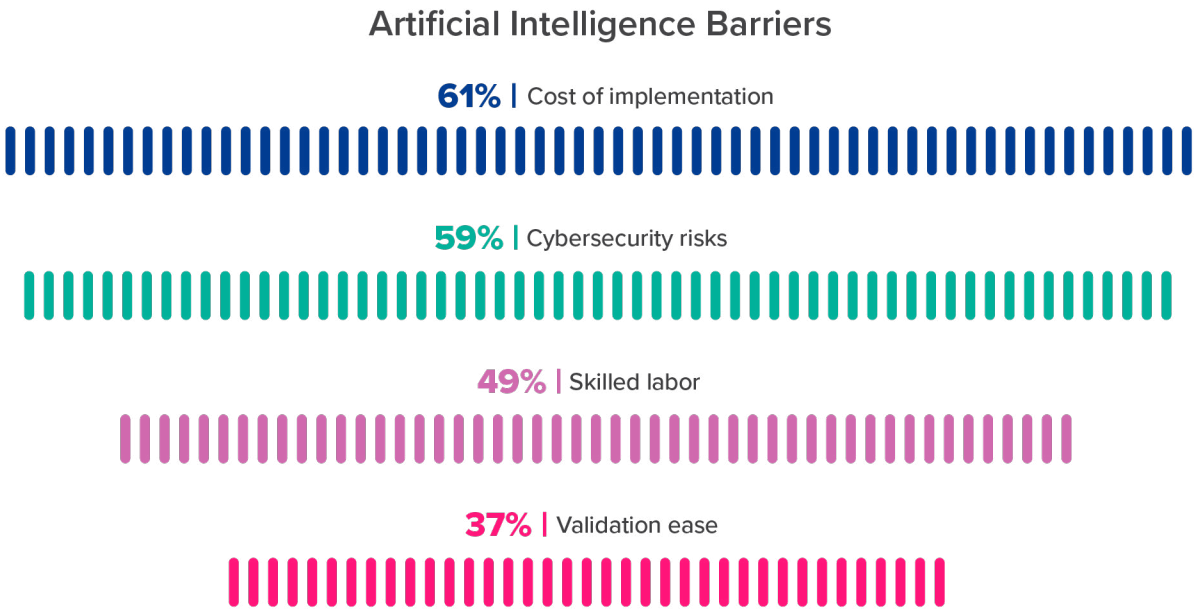
Moving from paper-based batch records to electronic batch record (EBR) can cost anywhere from $5–12 million. That includes putting in a manufacturing execution system (MES), which unlocks the ability to do EBR.

More than half of all respondents see cybersecurity risks, cost, and validation as the top concerns for implementing EBR (Figure 29.2). While the level of concern about cybersecurity risks between company types was similar, biopharma start-ups were much more concerned about cost (64%) than large pharma companies (36%). Interestingly, the situation was reversed for ease of validation, which more large-company respondents consider an issue (61%) than do start-ups (46%). This could well be due to the greater experience large companies have with regulatory agencies and the validation process.

The majority of all respondents across company type are rightly concerned about cybersecurity risks, though a rigorous pre-qualification strategy can help manufacturers manage this risk by identifying experienced vendors with excellent track records. As a case in point, one of our CMO clients hired a vendor to install an environmental monitoring system to track temperature and humidity during production throughout its facility and pull that data into its customer's batch records. The CMO made a poor engineering procurement decision, insisting on using a vendor that was not CFR Part 11 compliant. The vendor, which did not have experience working with pharmaceutical companies, installed a standalone system that lacked the necessary security measures and was not robust enough to withstand a security breach. Unfortunately, someone hacked into the CMO's batch record system, holding its customer data for ransom.

FIGURE 29.1

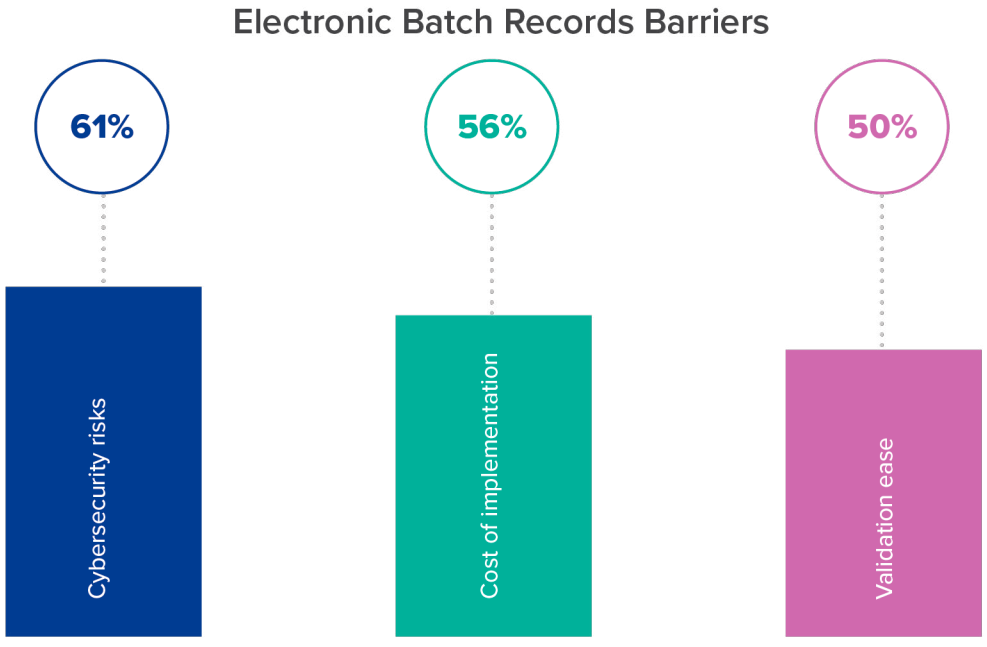
What are your barriers to implementing AI?



Source: CRB

FIGURE 29.2

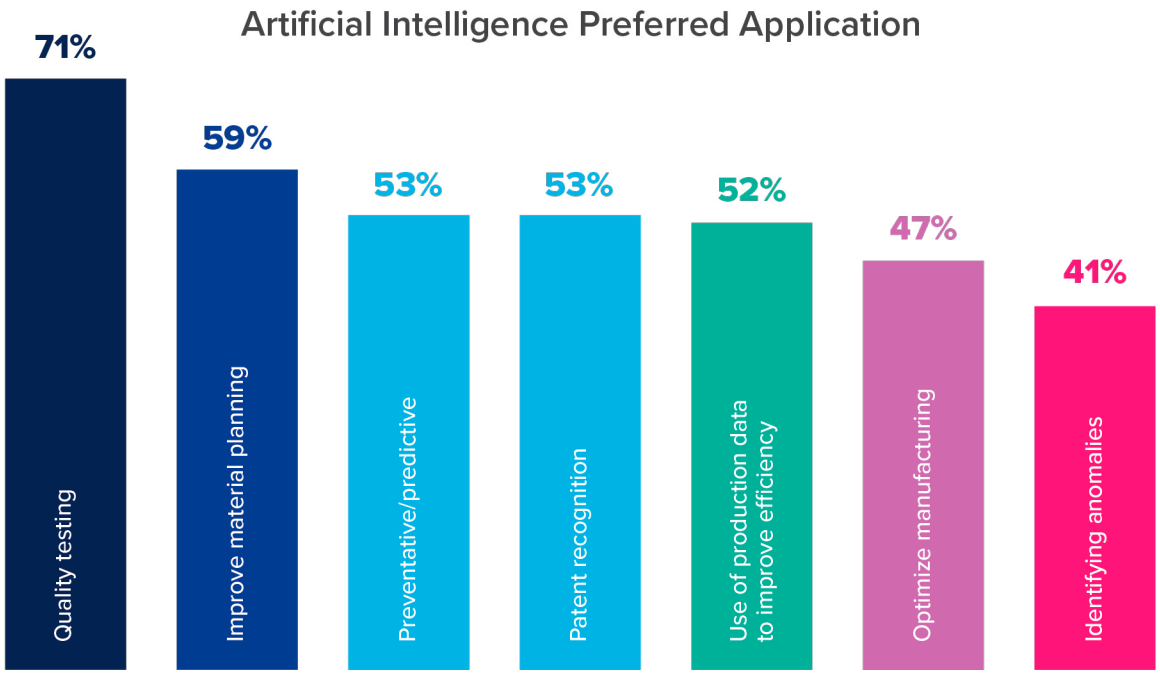
What are your barriers to implementing EBR?



Source: CRB

FIGURE 29.3

What are your preferred applications for AI?



Source: CRB

The bottom line:

Always ensure that a potential vendor deserves your trust by investigating its track record and fact-checking its claims. It should be CFR Part 11 compliant and have a history of working with pharmaceutical companies. Ask to see life cycle validation documents, such as the functional requirements specifications. A trustworthy vendor understands the regulations and how to ensure security in the pharma industry.

PHARMA 4.0™ CAN INCLUDE CONSTRUCTION 4.0, WITH DIGITAL TWINS AND AUGMENTED REALITY

An exciting aspect of Pharma 4.0™ is the role it is playing in virtual design and construction. Between 2014 and 2019, $25 billion was invested in construction technology. Since the pandemic—and largely because of the pandemic—construction technology implementation has been pushed an estimated five years ahead of schedule. By digitalizing the job site with tools that leverage virtual reality, 3D modeling, and

$25B

was invested in construction technology between 2014 and 2019

digital twins, project leaders stand to improve the speed and reliability of their design and construction cycles.

Construction 4.0 incorporates all the digitalization that has been applied at various stages throughout the manufacturing industry and brings it into a built environment, such as a pharmaceutical manufacturing facility. Most of the advanced construction companies are at Level 3, having moved beyond the data silos that can exist between design and construction teams. This allows them to transform the job site to resemble the manufacturing and assembly industry.

Digital twins, which are computerized replicas of a physical object or process, are already being used to duplicate operational and facilities information in such things as process control systems. They are also being applied to the design and construction of biopharma facilities as part of CRB's Construction 4.0 initiative. Augmented reality (AR) is being used for virtual construction visits and remote factory acceptance testing (FAT), the latter a trend accelerated by the pandemic. Given the relatively low cost, AR is a good starting point for incorporating aspects of Pharma 4.0™ into the construction process. And we're beginning to see the ease with which 3D printing is becoming possible in manufacturing and even construction.

There's been a mentality shift in design and construction from the traditional mindset of creating deliverables to asking, How do we assemble a building? It allows engineers to leverage the way they think to design in single-trade, multi-trade, and modular assemblies. In the near future it will allow the use of AI and machine learning to take design and construction data and really assemble it into automated and optimizational layouts. It will allow us to reduce part counts of a building. These are the technologies that are coming to our industry fast and furious.

Conclusion

The days of paper records are long gone, shown the door by the wide range of diverse and complex technologies involved in Pharma 4.0™. It can be daunting for a company wanting to rise to the next digital plant maturity level, but the rewards of having an integrated facility network, in which all aspects of the IT infrastructure talk to each other and share information, are immense.

Save a day, Save a life:

How will the “warp speed mindset” impact post-pandemic project delivery?

By Dominic Tate, Christa Myers, and Jarrod Wrampe



There’s not much the pandemic hasn’t changed, both within the pharmaceutical industry and outside of it. Traveling is different. Dining out is different. Working—whether remotely or in-person—is definitely different.

Some of what has changed is harder to see, but just as impactful. The general news-reading public, for one thing, became fluent in the language of “co-morbidities” and “mRNA vaccines”—a language that, until now, was largely the business of the pharma and healthcare industries. As people watched the race for a new vaccine unfold, they learned how that race works, and what goes into the drug development life cycle. As a result, enrollment in clinical trials rose, not only for COVID-19-related research but across many indications. VC funding climbed steeply over the last year and a half, too, particularly where personalized cell and gene therapy research is concerned. People are more involved than ever in the drug discovery pathway; they’re investing their bodies and their capital in the promise of preventative and curative medicine.

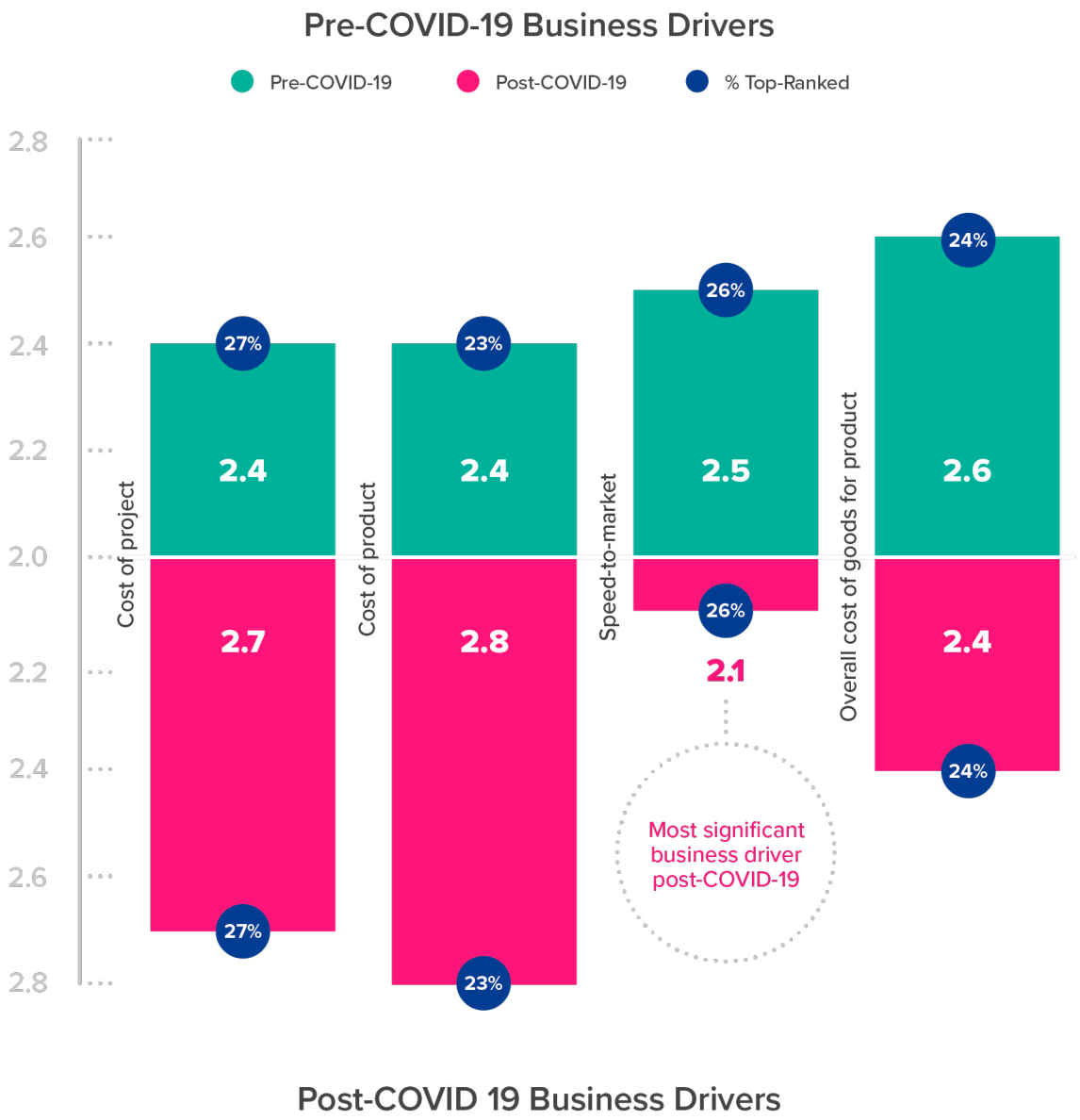
But how quickly will that promise become a mainstream reality? What has the industry learned over a year and a half of warp speed vaccine development, and will those lessons translate outside of the pandemic context to impact all drug discovery and manufacturing timelines? To find out, we asked our survey respondents what’s driving their business today, how they plan to keep up with the “new” pace of change, and what stands in their way.

IF SPEED MATTERED BEFORE, IT'S MISSION CRITICAL NOW

When we asked our survey respondents about their pre-pandemic business drivers, they ranked speed-to-market as their second-to-last priority as a whole. Post-pandemic, speed muscled into the top position, outranking other drivers by a long shot (Figure 30).

FIGURE 30

Pre- and post-pandemic, what were your most significant business drivers? One (1) is most important.



Source: CRB

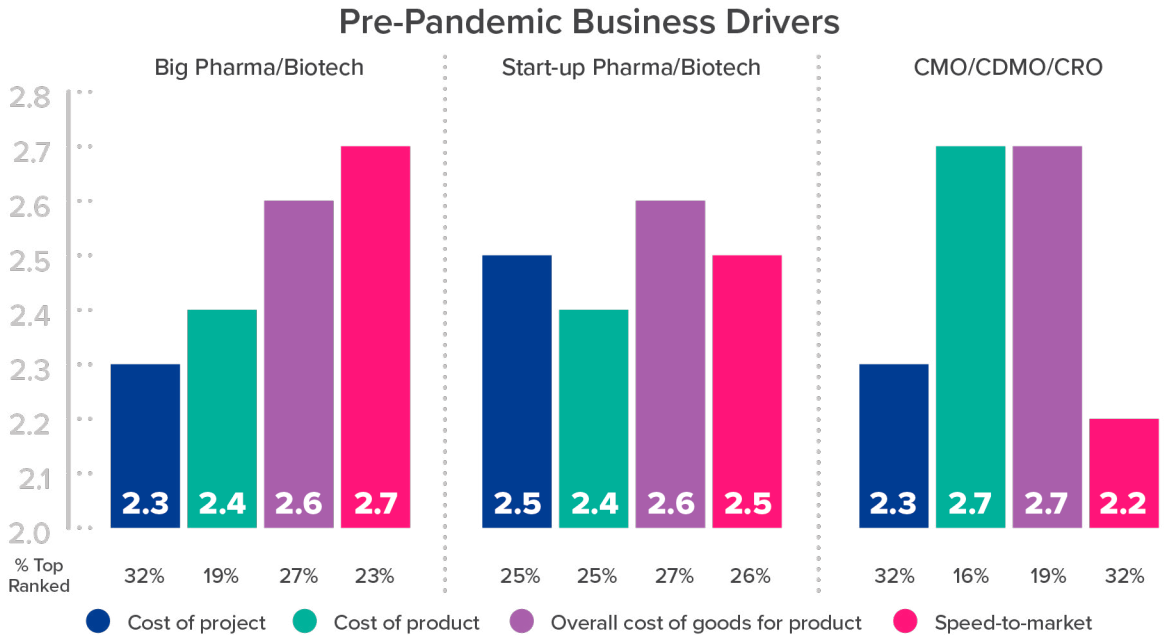
Look a little closer, however, and some interesting dynamics emerge. While CDMOs stayed relatively constant in their rankings for the pre- and post-pandemic contexts, we saw significant shifts from both large biopharma companies and smaller-scale start-ups alike—though these shifts showed up in different ways (Figure 31).

Large pharma companies ranked speed-to-market as the least important pre-pandemic business driver, while they identified cost of project as the most important. Post-pandemic, they flipped that hierarchy entirely. The volume of respondents who ranked speed as their top driver more than doubled, establishing it as the new top priority. Meanwhile, cost of project fell to last place, losing 21% of its pre-pandemic support as the top concern. Although cost of product and overall cost of goods stayed relatively constant as middle-ranked business drivers, the story here is clear: post-pandemic, large companies are under tremendous pressure to reach the market faster, even if it means spending more to get there.

Our start-up respondents followed a different journey to reach a similar destination. Unlike more established firms, speed was always a high-ranking business driver for them; pre-pandemic, it was second only to cost of product, and by a very narrow margin. Cost of goods, meanwhile, was their lowest-ranked business driver. Post-pandemic, something shifts: cost of product drops to last place while speed takes over that top-ranked position, and cost of goods climbs from least important to second-most important.

FIGURE 31

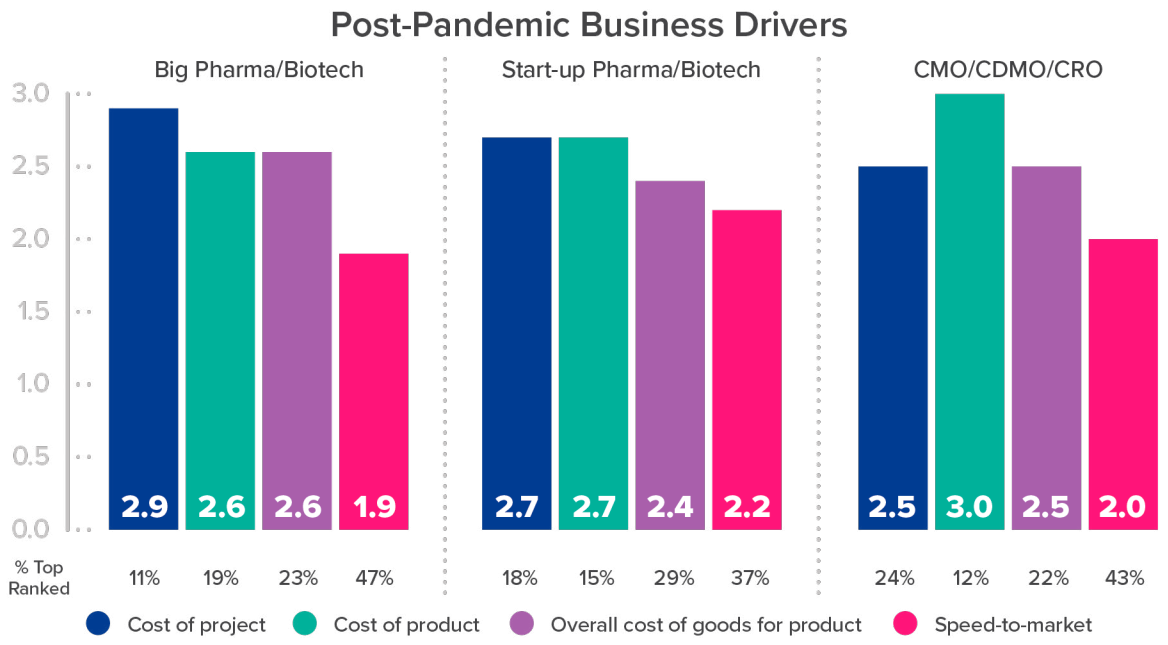
Pre-pandemic, what were your most significant business drivers focused on? One (1) is most important.



Source: CRB

FIGURE 31 (CONT.)

Post-pandemic, on what were your most significant business drivers focused? One (1) is most important.



Source: CRB

This makes sense. Unlike large pharma companies, who often have more opportunity to vertically integrate certain supply chain inputs, start-ups are almost entirely at the mercy of the open market. And when that market is as changeable and as constrained as it is today, cost of goods plays a significant role in determining the success or failure of a project. So, while they're responsible to their investors for moving as fast as possible, they're also under pressure to manage cost-related risks—which we see in their post-pandemic ranking of business drivers.

A SNAPSHOT OF POST-PANDEMIC PROJECT DELIVERY

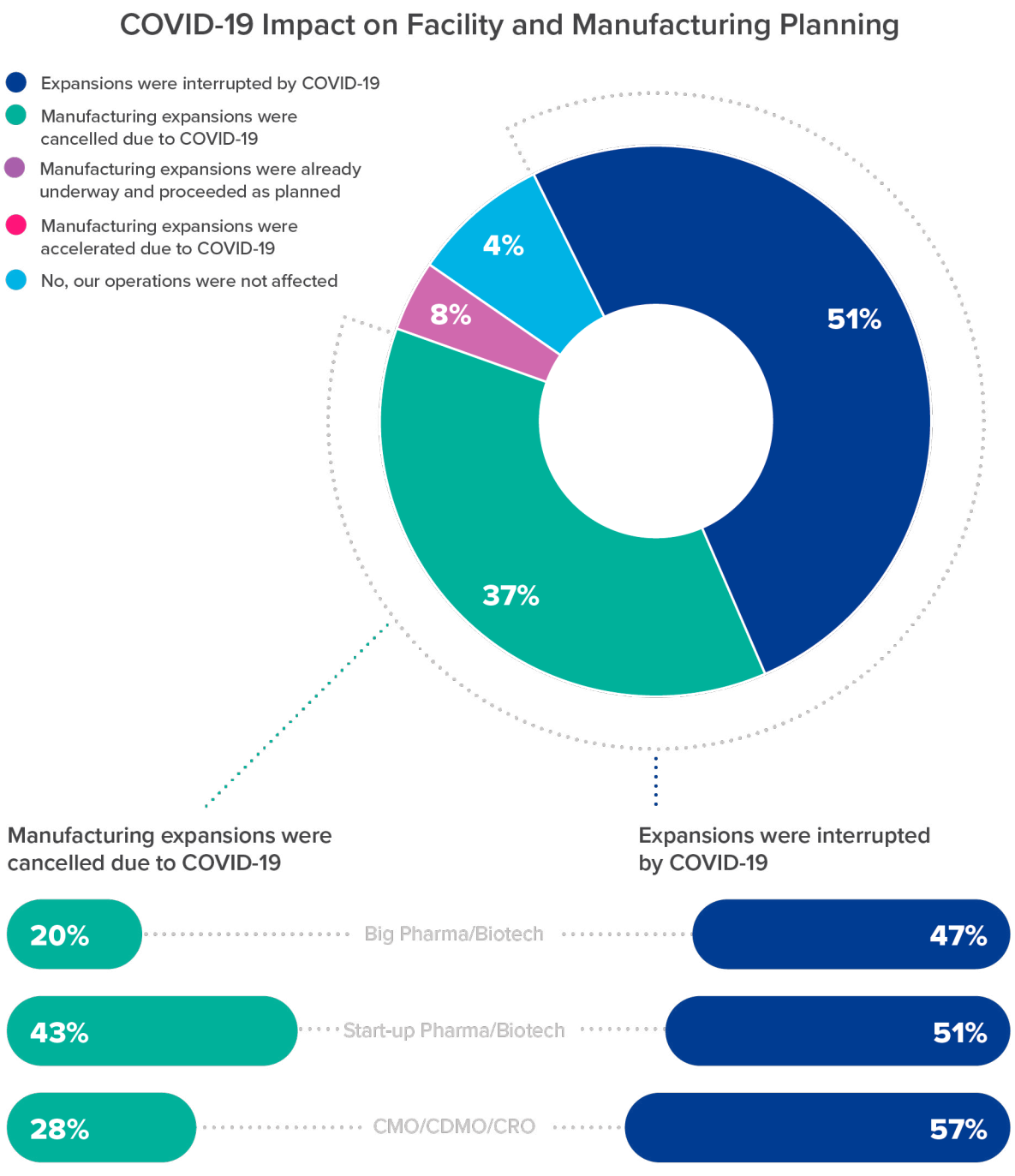
If most companies, large and small, are now driven mainly by speed, what does that mean for the future of capital planning and project delivery in the pharma industry?

It's no surprise that the majority of respondents reported some degree of negative impact to their expansion plans during the pandemic. For most, that impact took the form of an interruption in project delivery—some, though, had to cancel their projects altogether. That was the case for nearly half of all start-ups (43%). CDMOs were slightly less likely to have cancelled their expansion projects, while only a fifth of large pharma companies fell into that camp (Figure 32). This is likely because of the role played by larger pharma companies in the pandemic response; expansions rated by the Department of Defense under the Operation Warp Speed mandate proceeded at a record pace, with everything from building permits to construction materials to manufacturing-related consumables arriving faster than ever, and teams laboring

overnight on job sites, united by a sense of purpose and the world's compelling need for a vaccine.

FIGURE 32

How did COVID-19 affect your facility and manufacturing planning?

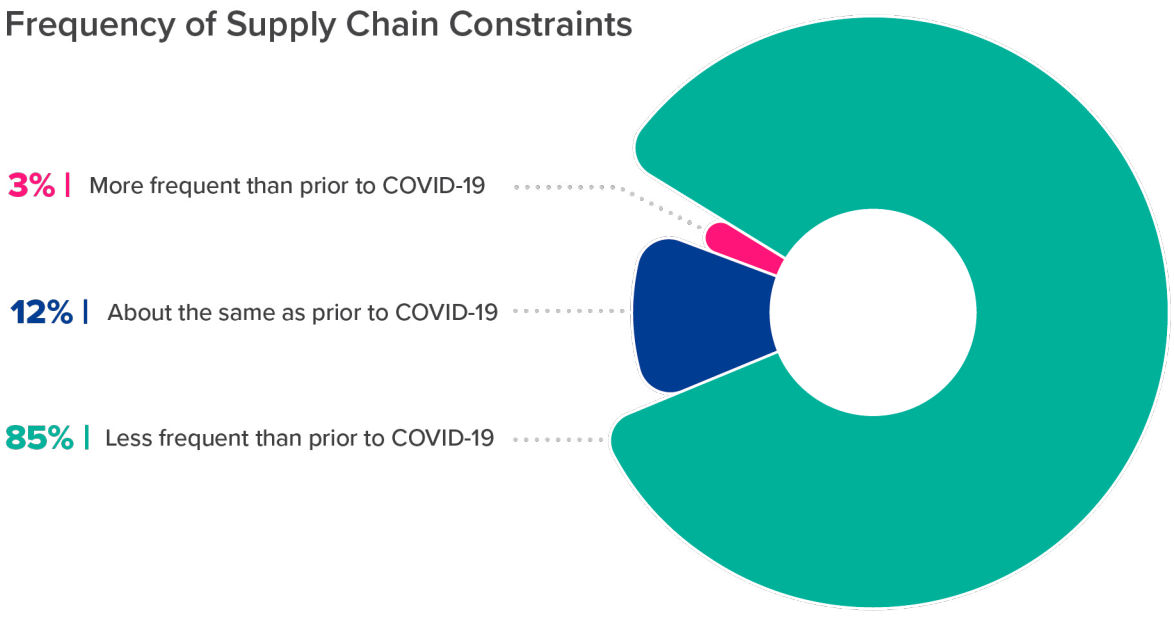


Source: CRB

That momentum seems to be catching. When we asked our respondents about their supply chain constraints, we learned that even those outside of the COVID-19-rated designation aren't experiencing challenges as frequently as they were before the pandemic (Figure 33). This could mean that after a year and a half of disruption, drug companies and their project delivery partners have developed new and flexible strategies to successfully navigate and de-risk their approach to accessing necessary resources. By putting those strategies in place early in the delivery process, companies can secure their access not only to building materials during construction, but to the manufacturing resources that are necessary for start-up and operation—resources like chemicals, commodities, and lab materials. These proactive strategies will help our industry meet today's project delivery demands, despite ongoing interruptions to the global supply chain.

FIGURE 33

Are your supply chain constraints more frequent or less frequent than prior to COVID-19?



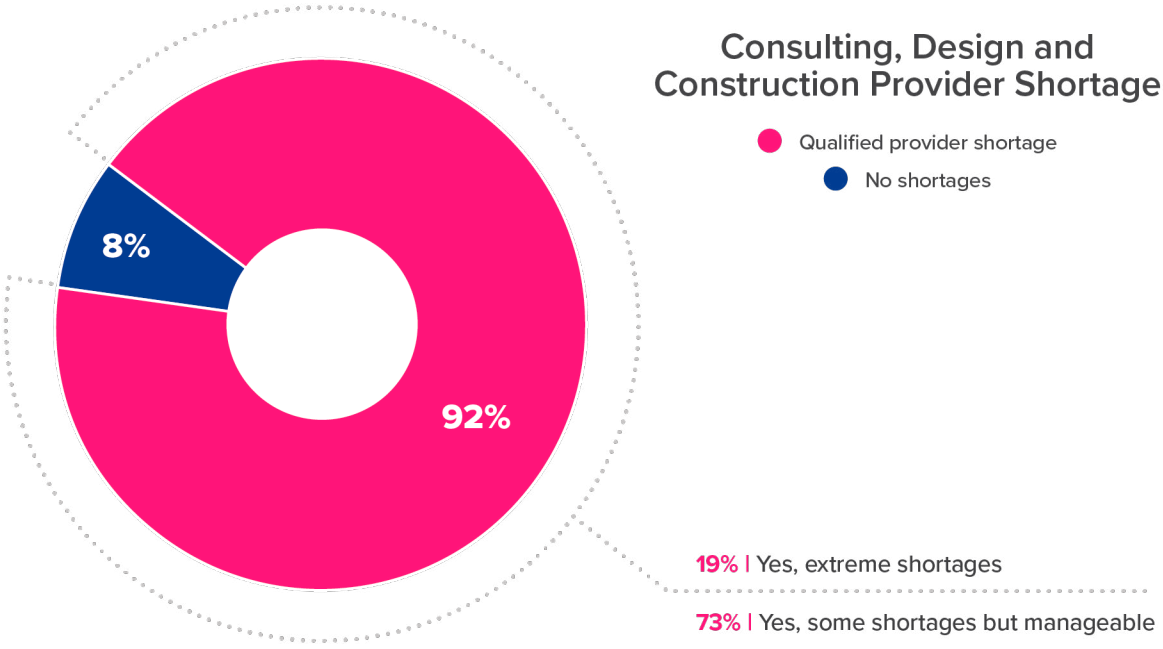
Source: CRB

This is good news, considering that project delivery activities are gradually returning to pre-pandemic levels. We can see this in our survey results: although their timelines may have shifted slightly, most respondents are busy planning long-term projects. Start-ups and CDMOs report an average delay of between three to five years in their capital planning strategy; large pharma companies report a slightly smaller impact, with survey respondents saying that most projects are delayed by between two to four years.

Two years is not long in capital delivery terms, and as many of these capital projects ramp up, companies of all sizes are now trying to establish relationships with the consulting, design, and construction partners they'll need to meet their speed-to-market goals. Some of them will find this difficult; as our survey shows, project delivery partners are in short supply, a constraint that's felt equally across companies of all sizes (Figure 34). How can project leaders address this shortage without further impacting their capital strategy timelines?

FIGURE 34

Have you experienced a shortage of qualified consulting, design, and construction providers?



Source: CRB

The answer is to find partners capable of keeping schedules on track by establishing a phased project delivery approach. Rather than closing the door on a manufacturer's capital project because they're at capacity, this type of flexible partner will tailor their delivery roadmap to align with both the manufacturer's target milestones and their own available resources. This could mean breaking the overall business case into discrete packages; if the goal is to have a facility with four production lines running at full capacity in five years, for example, a good partner might develop a plan to design and launch two production lines in the short term, leaving spare capacity for expansion over time. The manufacturer's goals are still met, but in a way that's realistic, controlled, and in tune with available resources and supply chain activity.

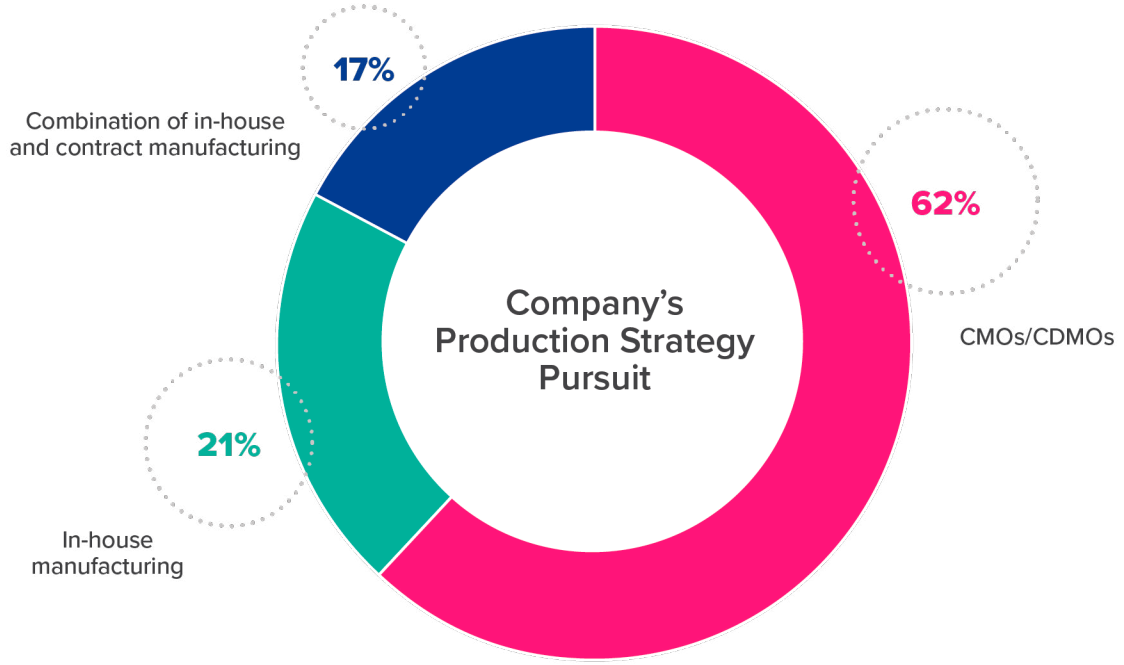
TO MOVE FAST, MAINTAIN FLEXIBILITY

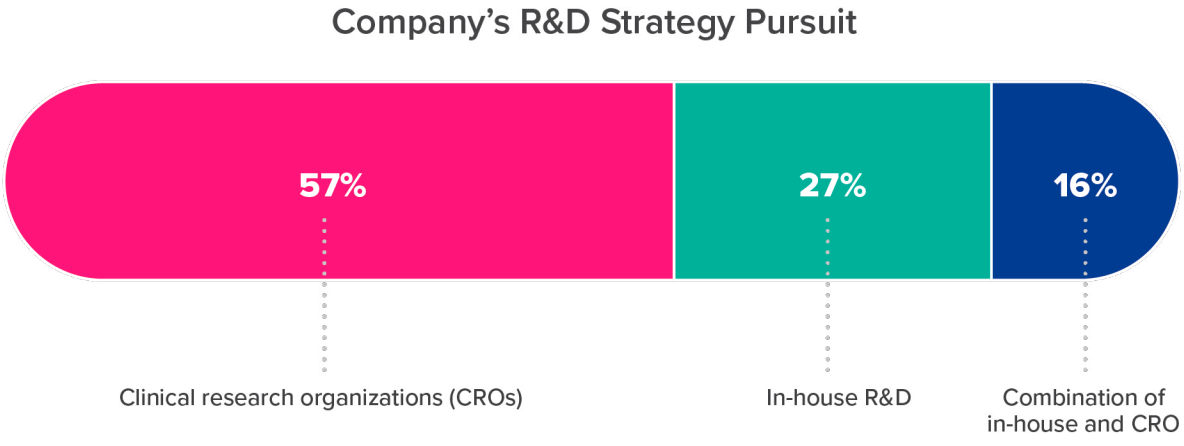
As capital project delivery ramps back up to pre-pandemic levels over the coming months and years, many companies are looking outside their own resources for strategic manufacturing and research support. On average, most of our survey respondents plan to lean exclusively on CMOs, CDMOs, and CROs (Figure 35).

FIGURE 35

[Top] In your company's production strategy, are you planning to pursue...?

[Bottom] Related to your company's R&D strategy, are you planning to pursue...?





Source: CRB

This isn't surprising, given the heroic role that CDMOs played during the push for a COVID-19 vaccine—a role which buffed their reputation to a shine and demonstrated that unprecedented speed and scalability are possible through strategic partnerships.

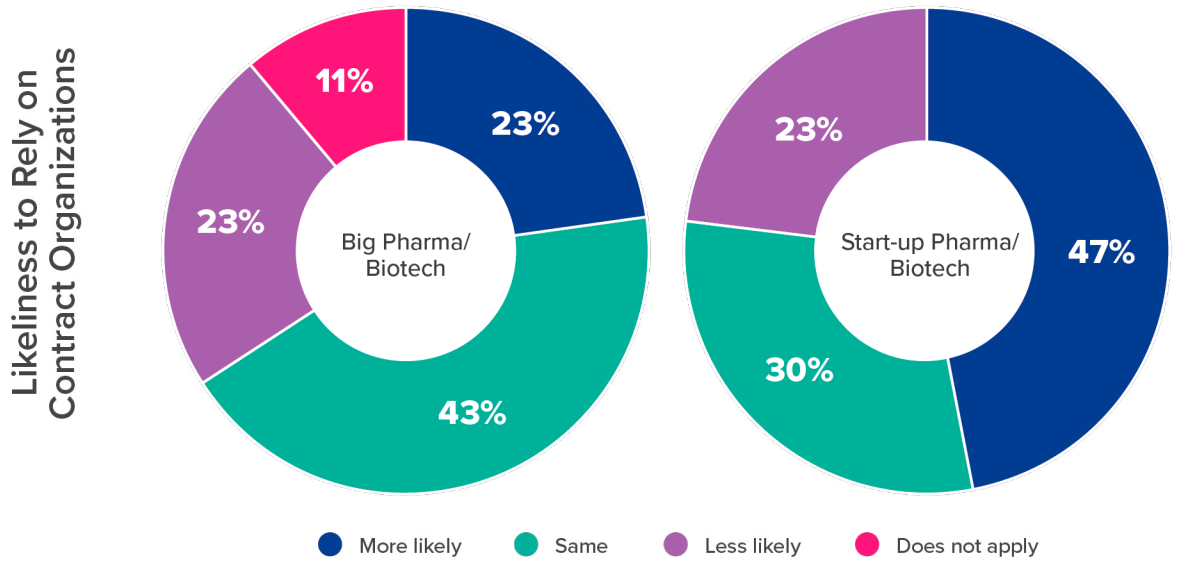
But companies whose scale-up strategy leans entirely on CMOs or CDMOs face a significant challenge: demand currently outstrips supply, and many contract manufacturers have prohibitively long lead times.

Large pharma companies seem to have planned for this in their manufacturing strategy. Our survey shows that nearly one-quarter of respondents say they're less likely to work with CMOs or CDMOs post-pandemic (Figure 36), and many of those who do contract out have a hybrid in-house/CDMO strategy. An equal proportion of large pharma companies work exclusively in-house. Only 18% rely on CDMOs exclusively (Figure 37).

Of course, large companies are better positioned than start-ups to limit their reliance on outsourced manufacturing. For one thing, they are more likely to have the capacity and the capital to vertically integrate certain operations, like the critical fill-finish step. Start-ups generally don't have this option as they scale toward commercialization. They're operating with less capital, less infrastructure, and a great deal of pressure from investors to get their product to market as fast as possible. That's likely why 73% of survey respondents from this group plan to rely on CMOs and CDMOs exclusively when it comes to production (Figure 37).

FIGURE 36

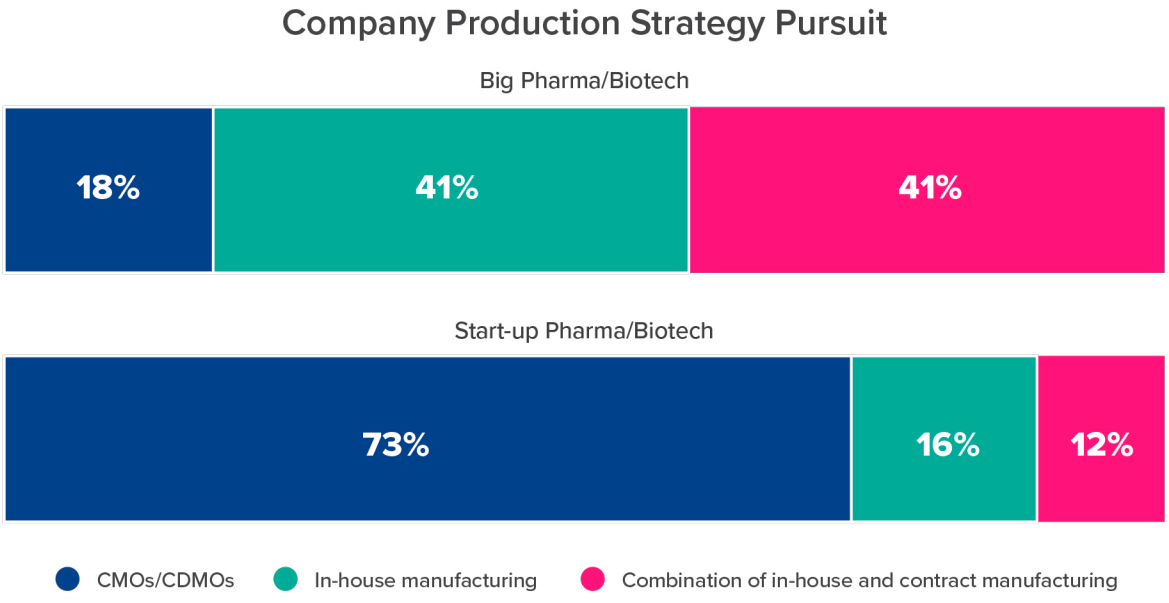
Has the pandemic made you more or less likely to rely on contract organizations in the future?



Source: CRB

FIGURE 37

In your company's production strategy, are you planning to pursue:



Source: CRB

Even with more CMOs and CDMOs coming into the market every day, how will so many start-ups compete for so few outsourced manufacturing slots? One way is to work with a consulting partner who can help them accelerate the process of finding, prequalifying, and negotiating with appropriate and available contract manufacturers.

A good partner will go even further, though, helping start-ups review their business case with alternative options in mind. If a drug developer faces a five-year wait for capacity with their CMO of choice, for example, but they could build a small-scale manufacturing operation in just two years, they may come out ahead; the value of getting their product to market three years sooner could more than offset the cost of constructing and operating their own commercial facility. And if they design future flexibility into that facility—by integrating multimodal equipment platforms, for example—then they could be at an even greater advantage, particularly as they grow and diversify their product portfolio over time.

De-risking these decisions requires complex financial modeling and an experienced perspective on what's happening right now in the industry, what will happen next, and how companies of all sizes can position themselves to turn rapid change and constant innovation to their advantage.

Conclusion

Moving COVID-19-related projects from kick-off to commercial manufacturing in record time required an enormous, coordinated effort, both from those inside the pharma industry and from the general public. Now that effort is shifting to impact the rest of pharma manufacturing, and companies of all sizes are seeking to leverage a “warp speed” state of mind to accelerate drug discovery and production so that more patients can survive their illness.

To succeed, these manufacturers will need a flexible, phased approach to project delivery—an approach that can withstand the pressures and turbulence of a market in constant motion without losing momentum.

An Open Door:
How the pandemic may have accelerated the growth of lean construction

By Mike Barrett and Carl Rohs

By now, it has become a truism: Nothing will be the same once the world finally shakes off the COVID-19 pandemic and the virus becomes just one more manageable endemic.

Name an institution, a favorite business, or a personal habit; chances are it won't resemble the status quo of late 2019 by the time we all shed our masks or trust handshakes with strangers again.

But what about the project delivery models preferred by the life sciences sector? Will they undergo a similar disruption? There's plenty of evidence to indicate significant dissatisfaction with the current dominant models—design-build (DB) and design-bid-build (DBB)—but the question of whether or not a shift to a "new normal" will accelerate adoption of lean approaches like integrated project delivery (IPD) remains open to debate.

THE TRADITION CONTINUES

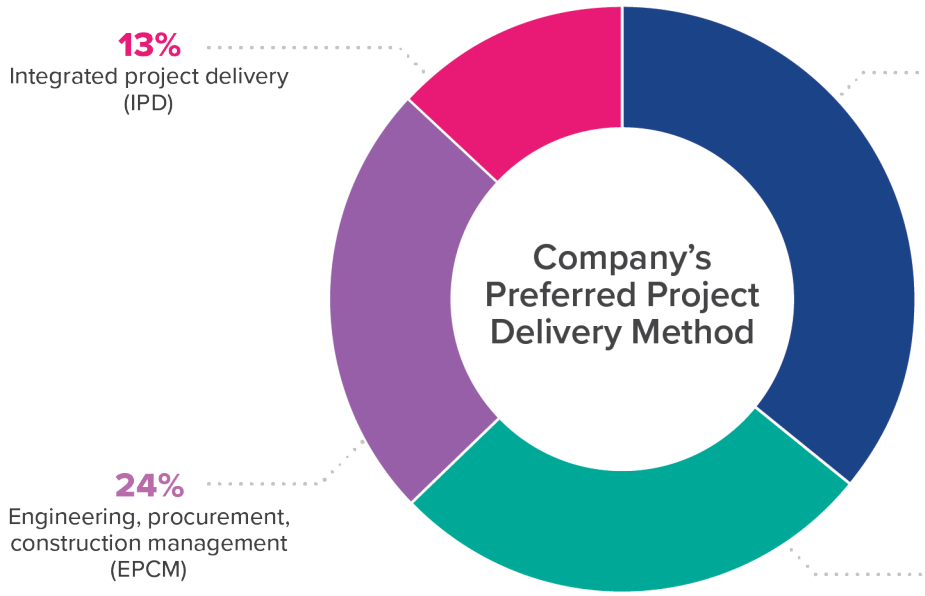
When we asked our survey respondents to rank their preferred delivery methods for large capital projects, DBB and DB pulled ahead as clear favorites (Figure 38). More than 60% of organizations continue to choose DB or DBB models for project delivery, with engineering, procurement, and construction management (EPCM) lagging slightly behind DBB, and IPD at just 13%. Only 6% of respondents at CMOs favored IPD.

only 6%

of respondents at CMOs favored IPD

FIGURE 38

What is your company's preferred project delivery method for large capital projects?



Source: CRB

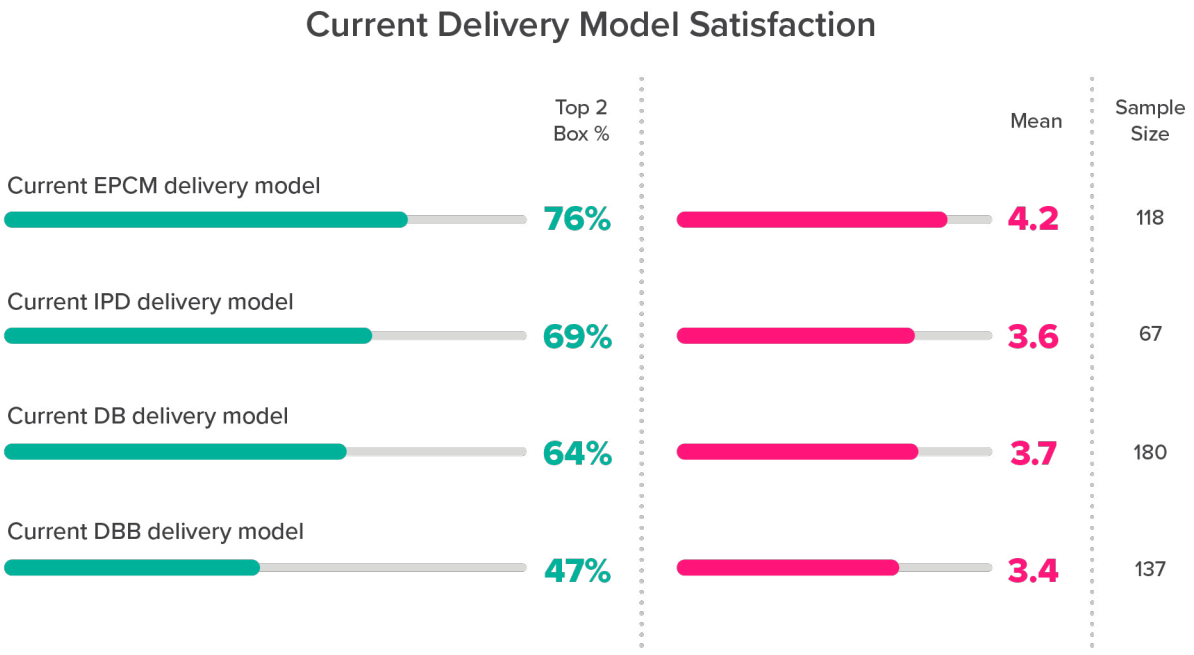
As the traditional models, DB and DBB have long-established benefits. There's no denying that the former can help drive projects to on-time delivery and provide a single point of responsibility. DBB continues to be popular with those who want a bidding process that's well defined and regulated, and it's designed to drive bid prices down and thereby secure a lower upfront cost.

But both approaches also have well-known drawbacks, as well. DB can require significantly more project oversight than other methods and places a large amount of risk in the hands of the project owner, or adds costs for embedded contingencies, like waste, if the risks are assumed by general contractors or contractors. While DBB helps companies minimize their initial capital spending, it increases the risk of cost and scheduling overruns, often leading to delays and a higher price tag overall. DBB also increases the risk for owners should cost overruns occur and has proven to be the most prone to litigation if things go wrong.

These downsides clearly aren't news for survey respondents (Figure 39). Less than half of those who use DBB are either extremely satisfied or somewhat satisfied with the model, while the same satisfaction rating for DB is under two-thirds, five percentage points behind IPD's ranking (with the proviso that the sample size is significantly smaller). DBB received a mean score of 3.4/5, DB ranked 3.7/5, and IPD averaged 3.6/5.

FIGURE 39

How satisfied are you with your traditional DBB current delivery model/current EPCM delivery model/current DB delivery model/current IPD delivery model? 1=Extremely dissatisfied, 5=Extremely satisfied.



Source: CRB

While the EPCM method ranked below DB and DBB for usage, those who do use it, like it. Its mean rating of 4.2/5 is encouraging, since, in many instances, EPCM has become something of a mesh of approaches, lifting some of IPD's collaborative approaches to create a hybrid. In fact, it's possible to view EPCM as "IPD lite"—a step toward full adoption of lean principles.

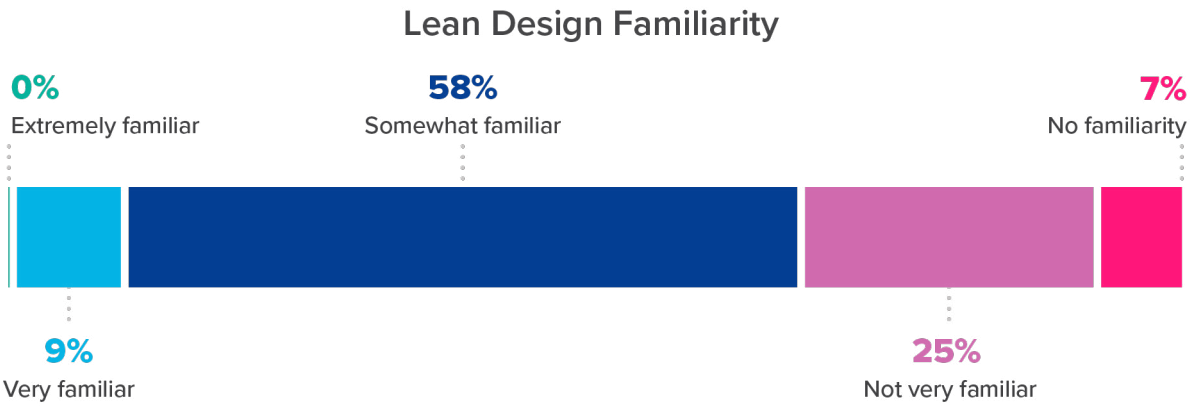
BACK OF THE PACK

It's no surprise to us to see IPD trailing the field; after all, the lean principles that underpin the model are still relatively new to pharma, and IPD itself has only been an alternative option for about a decade.

At this point, any step is still very small, however. Just 9% of respondents reported being "very familiar" with lean design (Figure 40) and no one responded that they were "extremely familiar" with it. It's worth noting that 20% of respondents at large pharmaceutical or biotechnology companies reported being "very familiar."

FIGURE 40

How familiar are you with "lean" design and construction project principles?

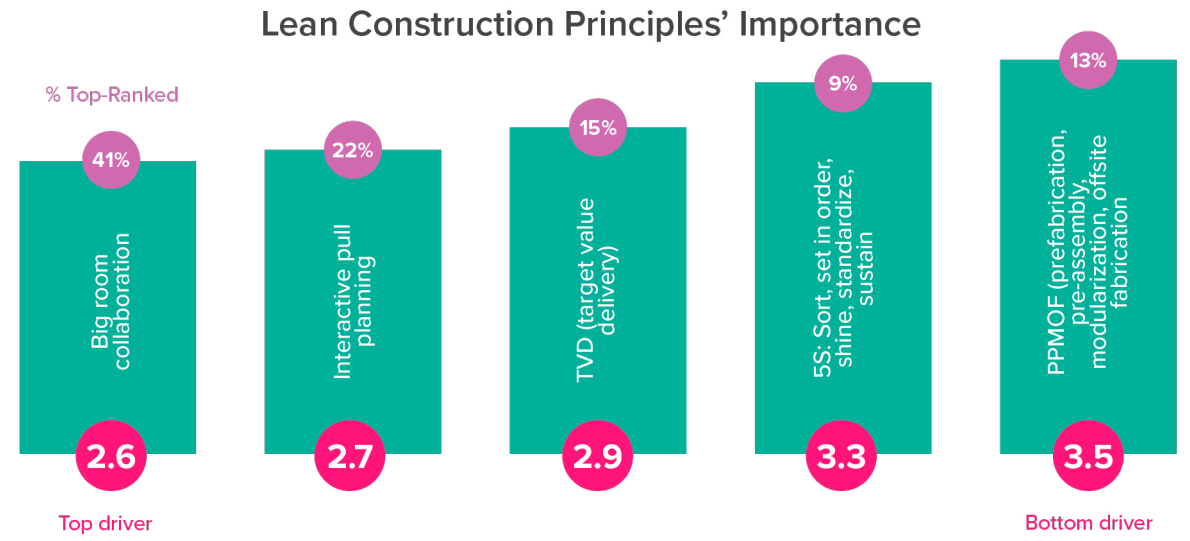


Source: CRB

In the course of said decade, however, IPD has made some inroads, as seen in the 58% bulge of those with some familiarity of lean design. Even more encouraging is that those familiar with the approach have a good handle on the importance of the collaborative nature of lean (Figure 41), placing that attribute well in front of other characteristics.

FIGURE 41

Of the following primary principles of lean construction, which do you consider the most important to a successful project?



Source: CRB

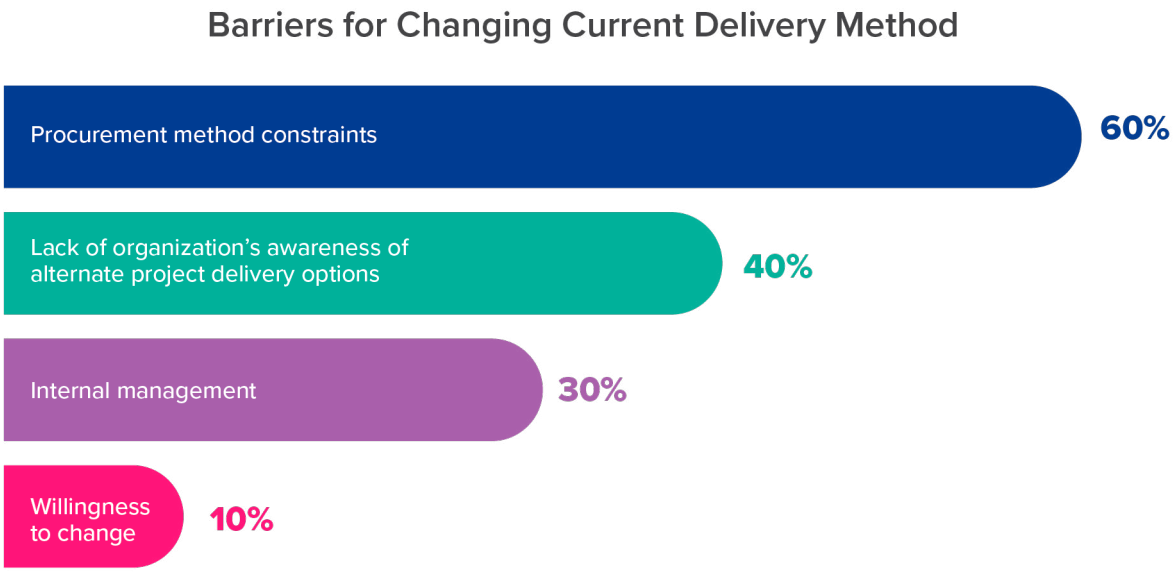
MIND THE GAP(S)

The disconnect between how many survey respondents rely on DB/DBB and how few report feeling satisfied with the outcome raises an obvious question: What's keeping organizations from moving—if not to IPD itself, at least in larger numbers to what we think of as IPD lite? In a word: procurement.

The survey shows there's willingness to change; 90% of respondents say their organizations are open to it (Figure 42). But 60% say procurement-method constraints are holding them back.

FIGURE 42

If you're not satisfied with your current delivery method, what are the top barriers to making a change?



Source: CRB

As noted, DBB places a lot of emphasis on the procurement process and both DBB and DB appeal to those who want the assurance of a good upfront price. But other sectors like healthcare and automotive and industrial manufacturing have shifted away from DBB toward IPD methods, and surely, they too are driven by cost control. So, what's holding pharma back?

In our experience, many companies also believe that the substantial amount of regulation in place on DBB projects helps to ensure fair, transparent bidding processes. In a highly regulated sector, a lot of additional work is needed to prove that you're compliant when attempting something new. If you want to consider why

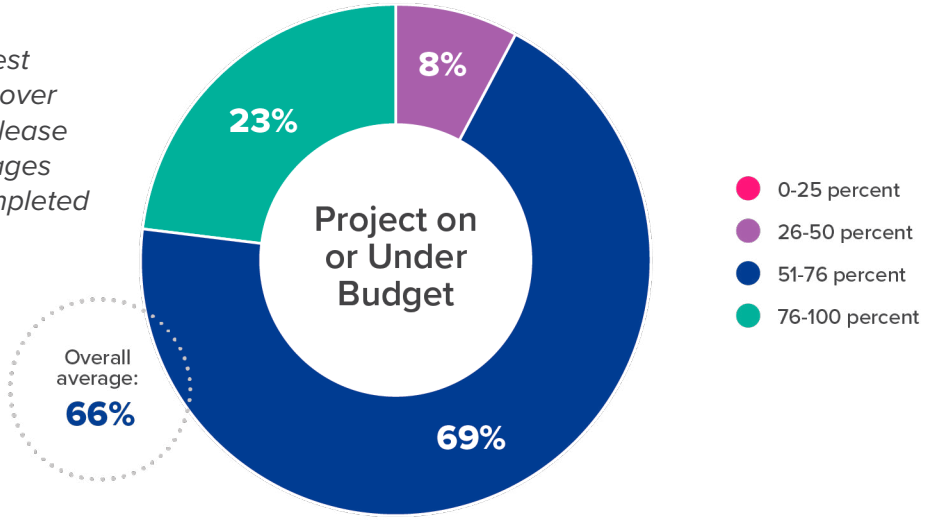
sectors like healthcare and automotive and industrial manufacturing have been faster to adopt IPD methods than pharma has, regulation is a good place to start.

Strong, effective regulatory oversight is all to the good, but too much focus on upfront pricing can preclude the benefits of collaboration, shared risk, and simultaneous implementation—to cite just three of the leading benefits of IPD.

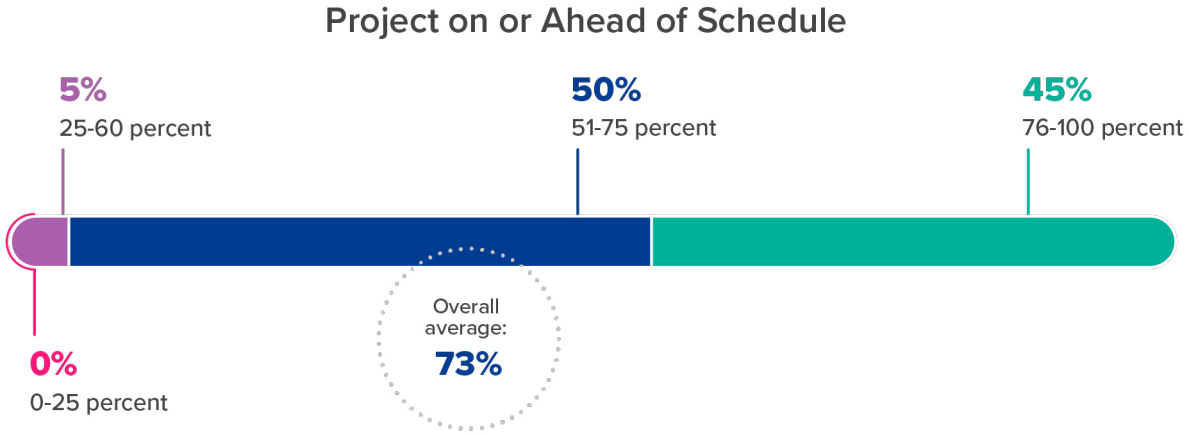
The fact is, a lot of the incumbent procurement leaders have lived their careers with DBB and DB, and they're reluctant to consider the alternatives. What's more, the way key performance indicators (KPIs) are structured at many organizations means there's no incentive for change. There may be some self-fulfilling prophecy at play, too. A pair of the survey's questions point to that (Figure 43).

FIGURE 43

Based on your highest performing projects over the last five years, please estimate in percentages how many were completed on or under budget.



Based on your highest performing projects over the last five years, please estimate in percentages how many were completed on or ahead of schedule.



Source: CRB

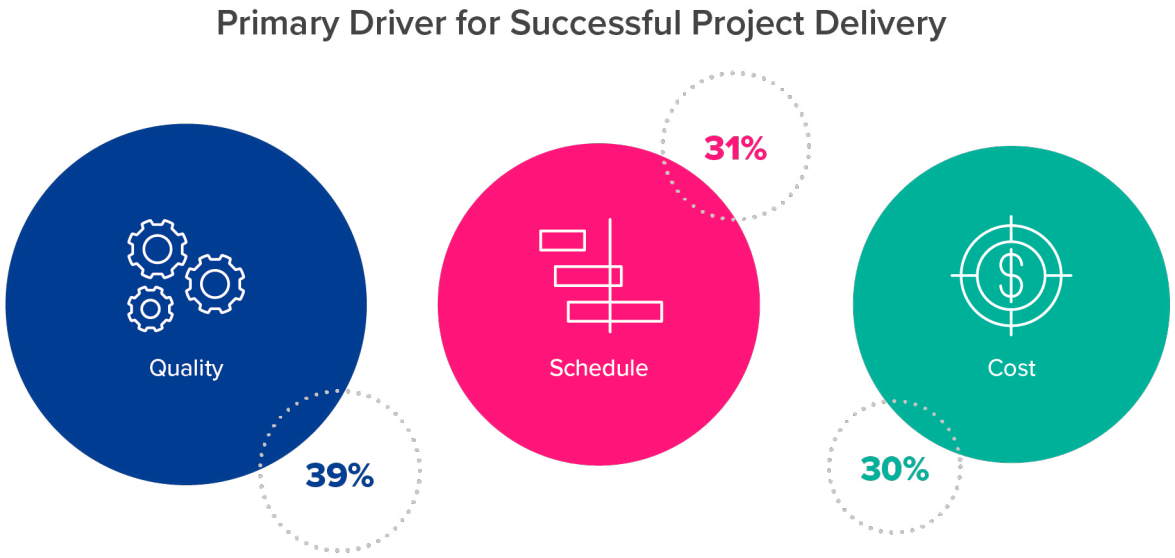
Very few respondents reported cost or scheduling overruns. Those findings, across a wide range of projects, frankly, run counter to our experience, and they seem to contradict the low level of satisfaction reported by respondents. So, what's going on here? First, there's the wording of the question—and the self-selection of top-performing projects. This could have skewed the results somewhat. But, in addition, it's quite likely that what respondents are seeing in their rearview mirrors may be colored by time and circumstance. For example, it's easy to forget how budgets were supplemented over the course of a project through change orders, or to overlook time extensions.

TRIPLE PLAY

If there's one major surprise in these results, and a finding that bodes well for those who recognize the many benefits of a lean approach, it's the fact that respondents ranked quality as the primary driver of successful project delivery (Figure 44).

FIGURE 44

What is your primary driver in the current market for successful project delivery?



Source: CRB

While it's heartening to see quality rank ahead of the pack, it's also encouraging that there's so little space between all three drivers. The overarching goal of a lean approach is to deliver projects that are on budget, on time, and that provide optimum quality. Because, speaking of truisms, a truly lean approach can deliver a win-win-win outcome. Seeing a close balance between quality, schedule, and cost here reassures us that there is movement in the sector, even if it isn't as fast as lean proponents may like.

Be nimble. Be quick. Be disruptive.

Where are we on the path to broader recognition of lean's benefits and wider adoption of its principles? We can't kid ourselves; if it's a 10-step path to universal acceptance of IPD, we're probably at about Step 3, and reaching full acceptance won't likely happen in this decade. But there is movement, and a clear recognition of the shortcomings of the traditional models.

It's probably safe to say that we all want to see some good come out of the past 18 months of tragedy, turmoil, and uncertainty. Within pharma, it's equally safe to say that quality and the ability to—it's unavoidable not to use the overused word—pivot rapidly have never been held in higher regard. The pandemic has opened the gates to welcome a different way of doing things.

There may well be a desire, and an opportunity, for more nimble facilities or micro-facilities that can be deployed more rapidly, and an accelerated path to an embrace of the lean method and the benefits it can deliver.

Project Delivery

SECTION THREE

To Accelerate from A to Z, try PPMOF:

For better speed-to-market, life science innovators need better project delivery tools.

By JP Bornholdt and Dennis Kearney

When it faced enormous pressure to move at warp speed toward a COVID-19 vaccine, the pharmaceutical industry deployed every tool in its belt. One of its most effective is the Swiss-army knife of rapid project delivery: prefabrication, preassembly, modularization, and offsite fabrication, or PPMOF.

Of the numerous pandemic-related projects that we collaborated on with our clients at CRB, roughly 90 percent relied on a PPMOF strategy to some degree. It was the best and most effective way to remove significant scheduling obstacles, deploy parallel workstreams, and ensure the quality and on-time delivery of key equipment platforms as we raced toward the finish line.

~90%

of CRB clients relied on PPMOF strategy for pandemic-related projects

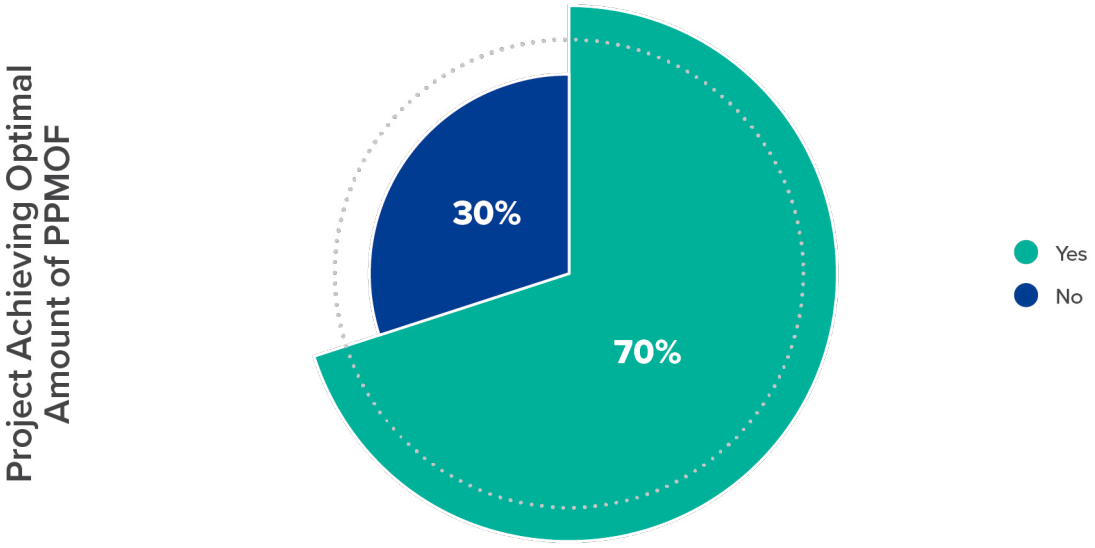
The world watched this unspool in real time, as strategies like PPMOF converged to deliver effective vaccines in less than a year. As we prepared our industry survey, we wondered if the success of this global warp speed initiative would change the way our industry approaches project delivery in general, and PPMOF in particular. Are life science leaders embracing PPMOF? If not, why not? In what ways are misconceptions about PPMOF keeping companies from meeting their scheduling and cost goals?

What we discovered is surprising. A large majority of survey respondents think they've got PPMOF "in the bag," so to speak—they believe they've done all there is to do (Figure 45). And yet only a mere 2% consider PPMOF "very" or "extremely"

valuable to their project delivery strategy (Figure 46). In the gap between these two statistics lies an opportunity to debunk outdated perceptions about modular design and explore exactly what it means to harness PPMOF in today's disruptive and unpredictable world of capital project delivery.

FIGURE 45

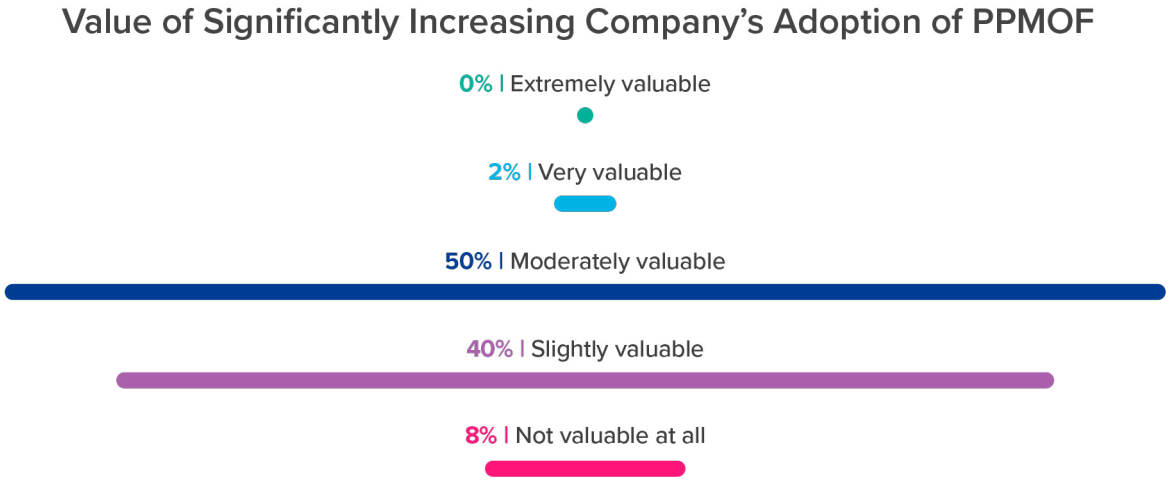
Do you feel that your projects are achieving an optimal amount of PPMOF?



Source: CRB

FIGURE 46

How valuable do you find significantly increasing your company's adoption of prefabrication, preassembly, modularization, and offsite fabrication (PPMOF)?

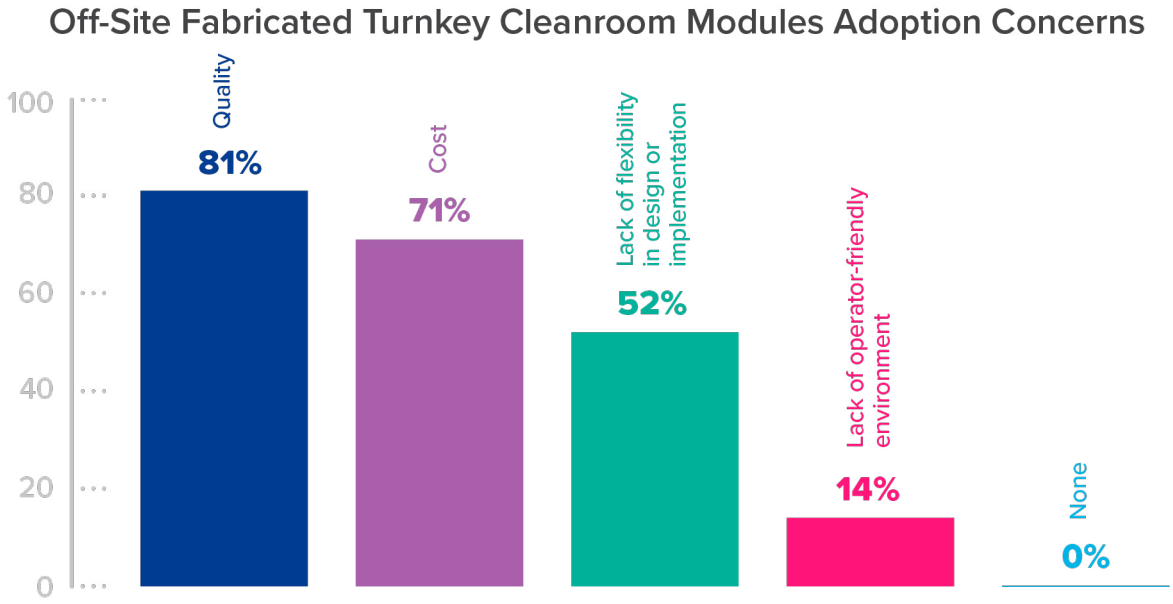


Source: CRB

Survey respondents named quality, cost, and a lack of flexibility among their top three perceived concerns for adopting off-site fabricated turnkey cleanrooms (Figure 47).

FIGURE 47

What do you believe are your organization's main perceived concerns when considering the adoption of off-site fabricated turnkey cleanroom modules? (Select all that apply).



Source: CRB

But some concerns carried more weight with start-ups compared to more established companies—like cost—while bigger firms ranked quality its top concern. Let's peel back the layers surrounding the biggest questions of PPMOF adoption.

WILL PPMOF MEET MY QUALITY EXPECTATIONS?

Everyone's anxious to maintain quality, but for large organizations, the stakes are enormous—93% of all survey respondents ranked quality as their top PPMOF adoption concern, compared to 79% for start-ups. PPMOF is making many wonder: Will I still get the quality and reliability I need from my facility if I modularize it and have parts of it prefabricated offsite?

The truth is, PPMOF can actually improve quality by mitigating risk and providing an early avenue to review and test systems ahead of time—and at different stages. Early equipment changes enhance quality before major production begins.

Skilled tradesmen and designers—partners you choose—make these changes in a fabrication shop,

93%

of large-company respondents ranked quality as their top PPMOF adoption concern

where they have total control over environmental conditions and can oversee assembly in real time. This translates to better scheduling control, giving you a timeline that allows for early reviews, including those from the FDA. These early reviews provide valuable guidance in terms of quality, efficiency, and regulatory concerns. So rather than putting quality at risk, modularizing actually provides a quality "safety net" and more opportunities to adjust.

A good PPMOF partner will also include services for managing issues as they arise. You're not ordering a clean room module and then forgetting about it until it shows up. There are virtual or face-to-face site visits and monitoring processes. These give you a chance to ask important questions: How are things working? Are we hitting our quality targets? If not, adjustments are made to certain components without disrupting other processes. That's the beauty of fabricating off-site.

Consider "quality" not only in how components are built and installed, but also how they're managed and monitored while operating. PPMOF isn't a new concept. Many international companies took the plunge a decade ago, realizing that a customizable standard kit of parts delivered the trinity of manufacturing: quality, timeliness, and affordability.

HOW CAN I JUSTIFY THE COST OF PPMOF?

For start-ups who are operating with tight cost controls and under the scrutiny of their investors, capital spending is top of mind: 76% list cost as their main concern related to PPMOF, compared to 55% for larger companies.

76%

of start-ups listed cost as their main concern related to PPMOF

In fact, PPMOF addresses cost sensitivities by shortening timelines and reducing the need for reconfiguration, allowing companies to recoup additional costs over the duration of the project and the life of the facility.

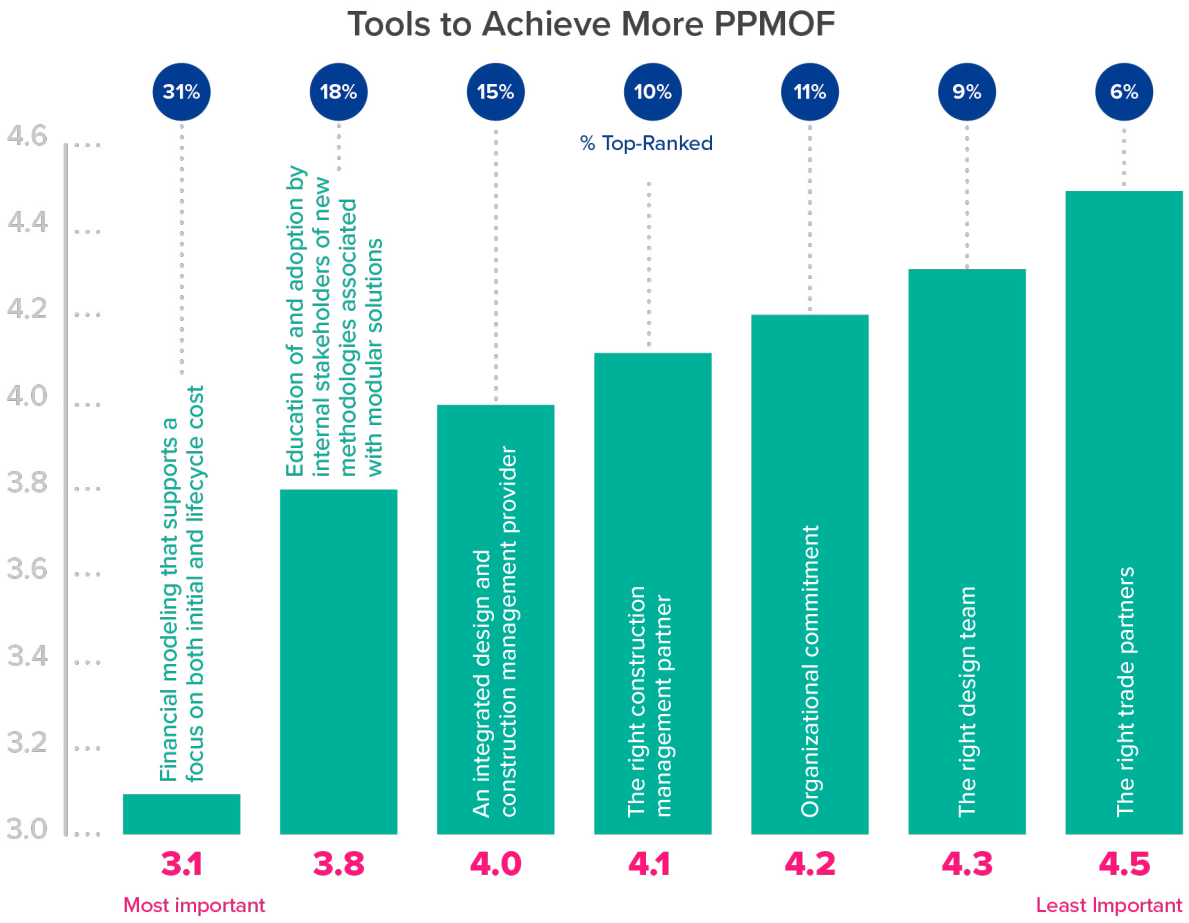
The cash timeline for procurement, integration, and build-out is actually very similar to traditional projects. Increased cost on a facility-wide level is only 3 to 5% for a modular offsite approach, according to multiple cost studies. It's only for "warp speed" projects that more cash is needed up front, in large part for equipment like boilers and chillers.

That first-cost increase is typically easily offset during the duration of construction as the timeline becomes significantly shorter than its traditional stick-building counterpart.

Survey respondents ranked financial modeling the most important among tools needed to achieve more PPMOF (Figure 48). Ranking second: education and adoption by internal stakeholders. Therefore, an important component of adoption is to quantify how potential additional costs are recouped.

FIGURE 48

What do you see as the most important tools to achieve PPMOF?



Source: CRB

As far as justifying the slightly higher cost for PPMOF: large pharma companies manufactured a successful vaccine through modularization, and now they've moved with confidence to other projects like COVID-19 boosters. PPMOF adoption facilitated their success.

WILL I HAVE TO GIVE UP FLEXIBILITY?

Flexibility ranked third in PPMOF adoption concerns for 52% (61% of big firms compared to 48% for start-ups). It makes sense that companies are skittish about the idea of not being able to make changes, but modularization is customizable—very customizable. The rigidity assumption comes from the stigma of what most consider when they hear the word "modular."

Let's use the example of a modular home. Most people think a stick-built home is better quality than a modular alternative. And when it comes to residential construction, they're often right. But a modular home and a modular manufacturing facility have very little in common. A modular home is buying what's already designed and built. When you invest in PPMOF, you aren't getting off-the-shelf, cookie-cutter solutions. You're driving the design—from vetting and choosing trade partners to making and overseeing changes.

Just one sentence forms the flexibility argument against modularization in manufacturing: "It's mass production."

It is—of a few basic components. Some of the world's most innovative companies harness this methodology. Think Tesla. Or the Apple iPhone. Think of the pre-planning and design, the number of people who weigh in and suggest changes. All of that input generates best practices which Tesla or Apple innovators can efficiently apply across their product lines—with resounding success. It's like building with Lego blocks: the individual components are standard, but you can assemble those parts in whatever way you need to accomplish your goal on time without sacrificing quality or budget. PPMOF is the same idea for the manufacturing industry, except it's tailored for specific products, companies, timelines, and design. It's truly the best of both worlds—the efficiency of leveraging all the pre-work and discovery that came before you, and the flexibility of making tailored changes to suit your particular project.

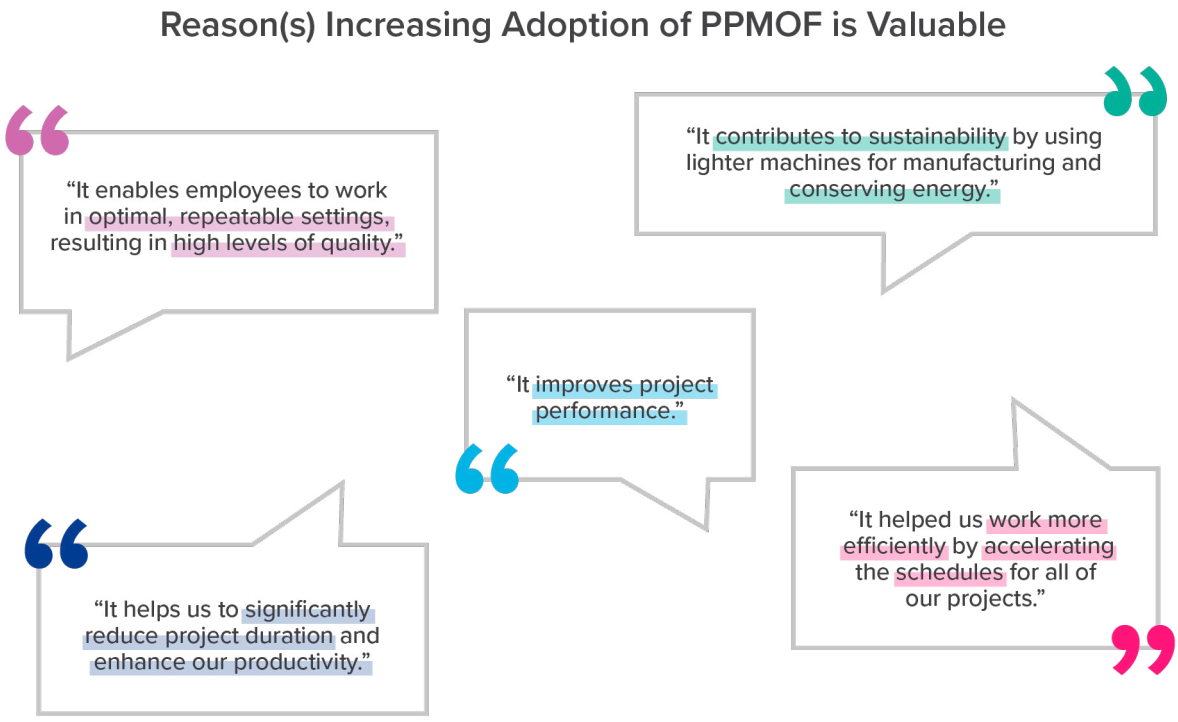
Bottom line: PPMOF is not just a fad.

The hesitation surrounding PPMOF adoption revolves around its relative newness. The "We've always done it this way" is a common refrain. Data points indicate many are waiting for things to go back to "normal."

But this is very likely the new normal. Disruption. Now, consumers expect to have vaccines and medicine quickly. They expect grocery store shelves to be full. The past two years revealed weaknesses in the supply chain across industries that are ongoing—biopharma, food manufacturing, goods manufacturing, construction. Large biopharma companies adopted PPMOF, with positive experiences (Figure 49). And it will also work for smaller companies across industries.

FIGURE 49

Why do you see value in significantly increasing your company's adoption of prefabrication, preassembly, modularization and offsite fabrication?



Source: CRB

It doesn't make sense to go backward.

The new normal demands innovation and practicality, figuring out how to prevent delays and bottlenecks—or at least reduce them. PPMOF adoption is the way forward.

A Comprehensive Approach to Sustainability:

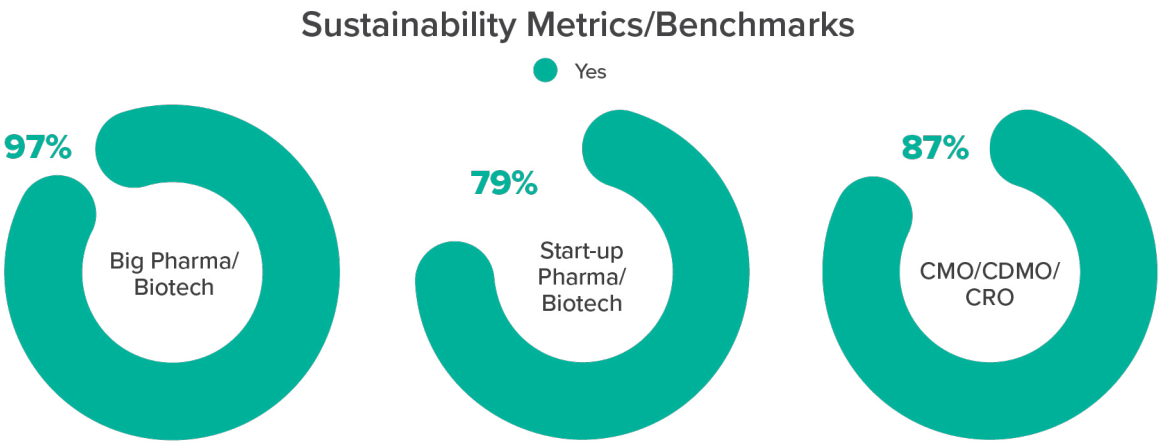
Why it's no longer just a nice-to-have

By Jeff Wegner and Maya DeHart

It will be of little surprise to any reader that large biopharma companies have committed to sustainability metrics at both the corporate and project level. What might be more surprising is the fact that companies of all sizes, including start-ups, are making these commitments as well (Figure 50).

FIGURE 50

Does your company have formalized sustainability metrics or benchmarks that it is measuring against?



Source: CRB

What's driving these commitments, and what's changed over the last few years? In our opinion, there are three factors behind the trend:

1 **REGULATORY ENVIRONMENTS**

Led by states like California, regulators are updating building codes to incentivize energy efficiency. Examples include electric heat pump technology as a replacement to gas-powered systems and expanding solar photovoltaic (PV) systems and battery storage to drive businesses to have clean energy available onsite. Other states are following California's lead.

2 **CUSTOMER AND SHAREHOLDER EXPECTATIONS**

Climate change is filling daily news feeds, and customers and shareholders alike are increasingly demanding that companies demonstrate their efforts to reduce carbon emissions. This filters down the supply chain for larger businesses, with many now including sustainability measures and reporting as part of procurement and partnership processes.

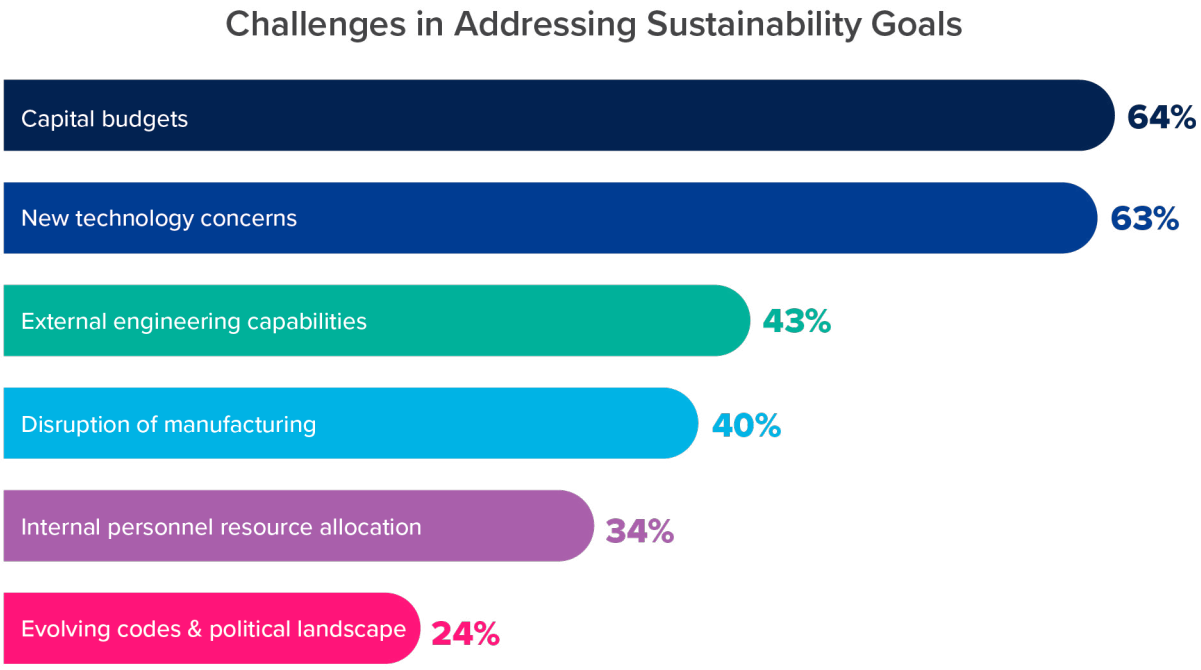
3 **TECHNOLOGY HAS MOVED FROM A POSITION OF COST TO ONE OF SAVING**

We're at a point now where many technologies are bringing costs down; solar is a great example. Biotech and pharmaceutical companies are electricity intensive, and the good news is that electricity is becoming greener and more affordable. Add PV and thermal or battery storage onsite, and it's good for the bottom line as well as the environment.

Although the commitment is there, and some sustainable technologies are becoming mainstream, cost does remain an issue. While 82% of all companies surveyed have funding to support their goals, 64% list capital budgets as a major challenge to meeting them. In short: there is money, but not enough (Figure 51).

FIGURE 51

What do you see as the most significant challenges in addressing your company's sustainability goals?



Source: CRB

A BROADER DEFINITION OF SUSTAINABILITY: PLANET + PEOPLE + PROFIT

When asked about the meaning of 'sustainability', most survey respondents included traditional answers around environmental impact; resources, carbon, and efficiency, for example. Out in the field, however, our team finds that profit is an essential calculation for most companies, and the 'people' part of the equation is becoming increasingly important. Our survey highlights this experience.

- Employee health and wellness is becoming an essential element of company policy. In fact, every last respondent reports having some kind of plan related to this issue, and that plan is concrete and well-defined for more than half of all respondents (Figure 53.1).
- Companies are very slowly starting to realize that while funding is still a challenge, there is an opportunity cost associated with NOT directing efforts toward sustainability. With 44% of respondents including supply/value chain as part of carbon footprint metrics, it's clear that ignoring sustainability initiatives will be a disadvantage in a competitive bid process (Figure 54).

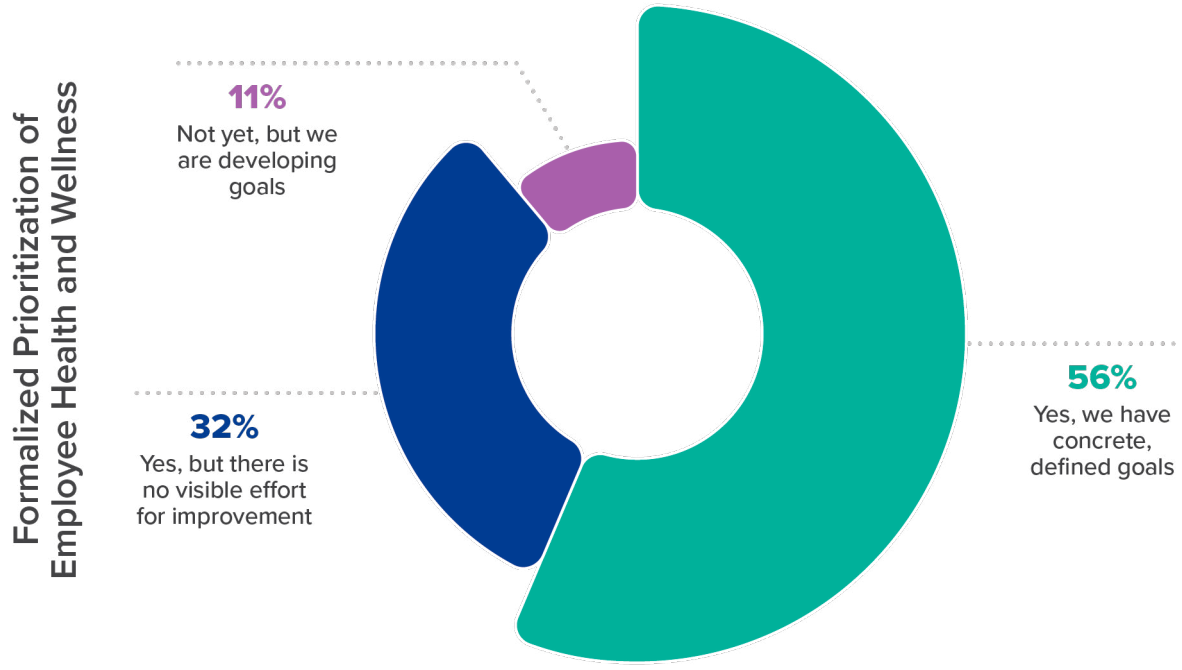
FIGURE 52

In one word, what does sustainability mean to you?

Source: CRB

FIGURE 53.1

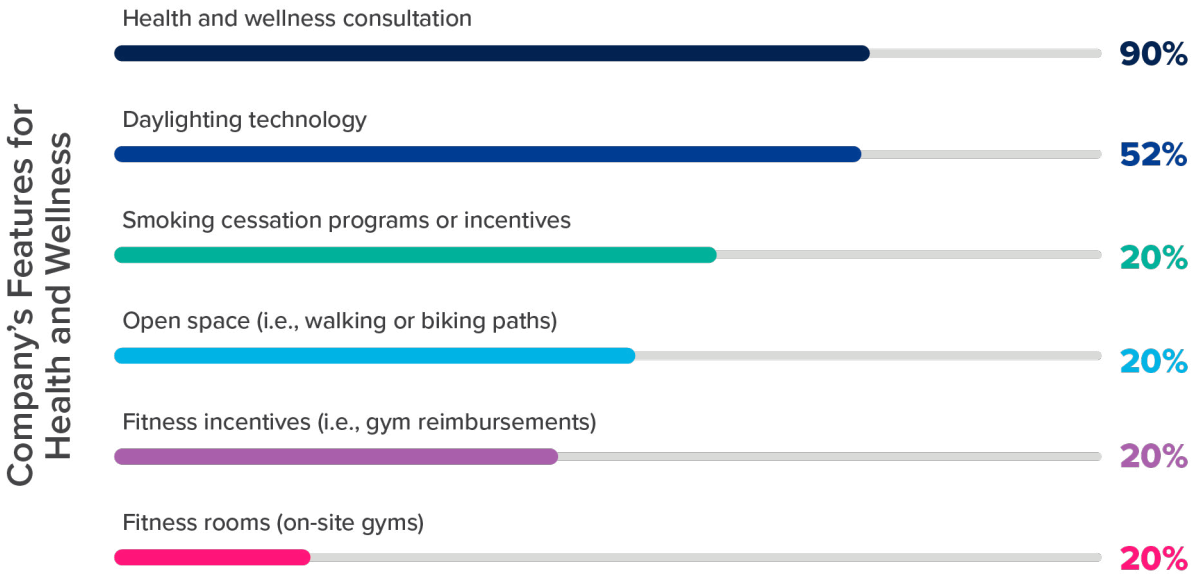
Does your company have formalized prioritization of employee health and wellness?



Source: CRB

FIGURE 53.2

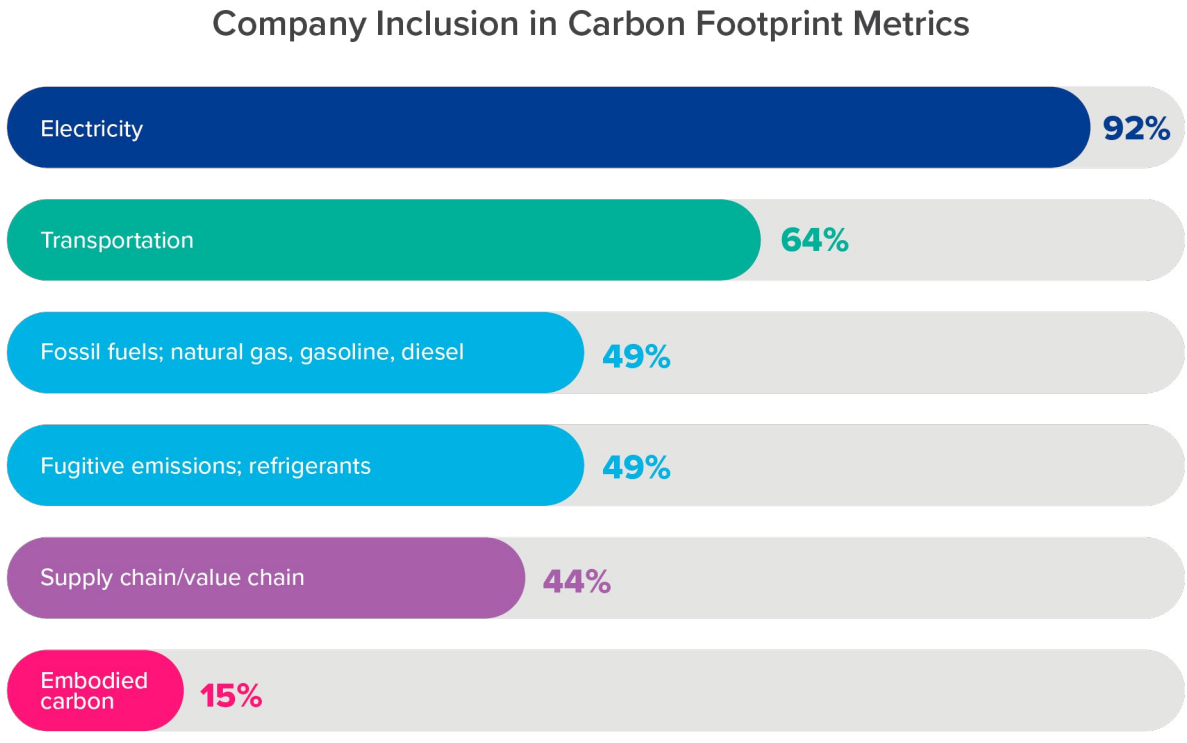
What features has your company incorporated that are aimed at the health and wellness of the workforce?



Source: CRB

FIGURE 54

What does your company include in its carbon footprint metrics?



Source: CRB

PLANET

When it comes to formalized sustainability benchmarks, companies of all sizes—from multinational pharmaceutical manufacturers down to tiny start-ups—are on board (Figure 50). Interestingly, regardless of size, respondents are committing at all levels of the company. At the corporate tier, carbon footprint metrics feature the greening of electricity (92%) and transportation (64%) (Figure 54). Right now, these are easy wins. With electricity suppliers greening the grid, companies have to do very little to report good numbers on this front. Likewise, the introduction of multi-modal transportation, reducing reliance on truck and air and increasing rail and marine, make emissions savings on transportation an accessible target.

64%

of respondents reported that securing capital budgets is a barrier

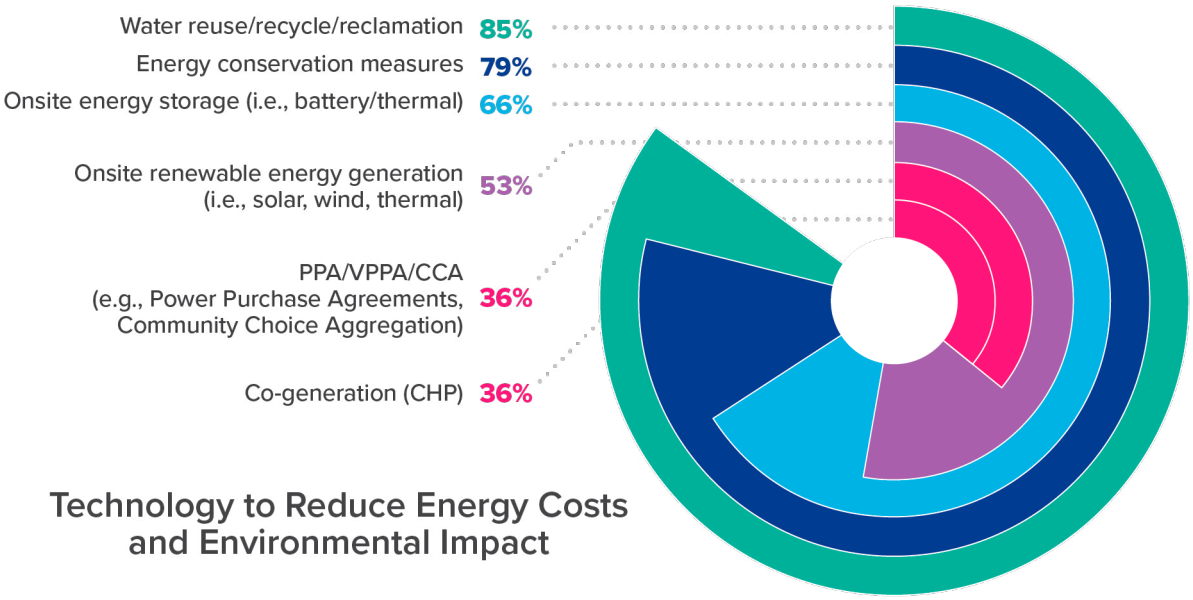
What's holding companies back? Again, funding is an issue. Although 82% of companies reported having specific funding to address sustainability goals, 64% reported that securing capital budgets is a barrier. New technology concerns are reported as almost equally prohibitive, at 63% (Figure 51).

Concerns about new technology are legitimate, and we'd be surprised to find a company that says otherwise. Traditional natural gas-fired equipment, for example, is tried and tested, backed by decades of results and maintenance teams equipped to handle issues. Switching to newer, forward-thinking technology like heat pumps and electrics takes some fortitude, since it's a significant investment and requires careful planning.

That being said, water and waste technologies rank highly on the consideration list as energy conservation measures (Figure 55). This marries well to respondents indicating that water and waste are the most important sustainability categories (Figure 56). We might interpret this in two ways; one being that the technologies have a lengthier history, so companies are more comfortable leveraging these to make inroads on environmental impact. Alternatively, it may be that the trend toward single-use technology is a driver here. As the industry moves toward this approach, there is a trade-off happening. Water and energy use is reduced, which has a downstream effect on the required utility systems. However, solid waste increases, making recycling and efficient waste management essential.

FIGURE 55

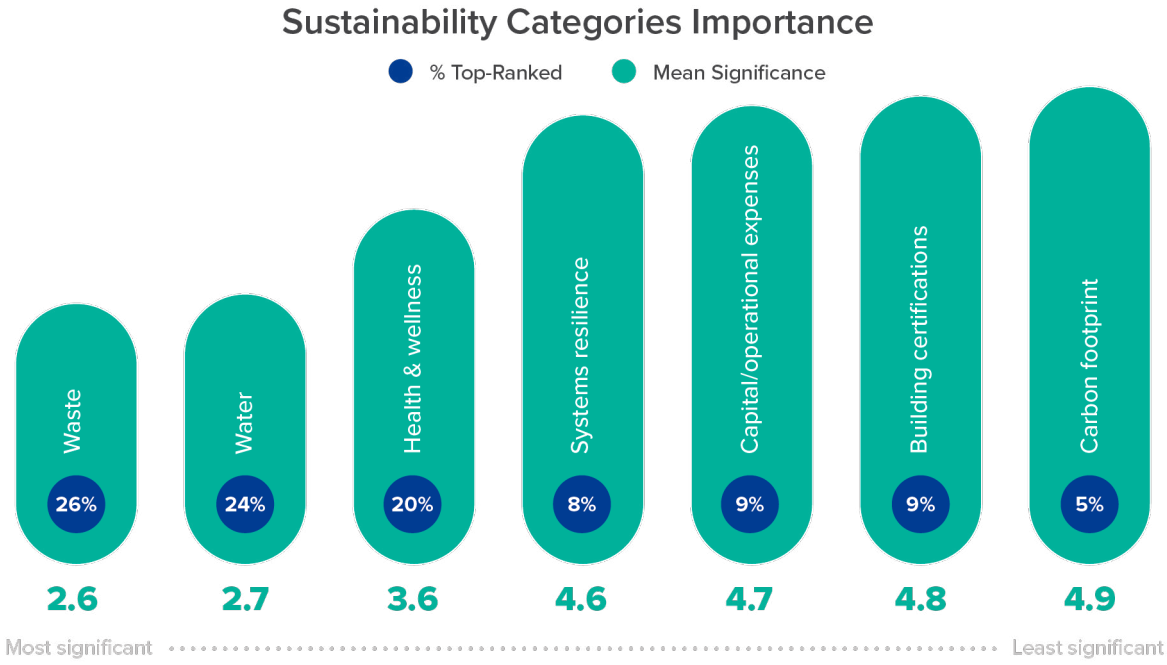
What technologies would you consider as a means of reducing energy costs and improving environmental impacts?



Source: CRB

FIGURE 56

Rank, in order of importance, the following sustainability categories.



Source: CRB

PEOPLE

In recent years, as companies have moved to establish Environment, Social, and Governance (ESG) practices as a way to create value, employee health and wellness initiatives have exploded. Of the 500+ survey respondents, every one of them reports having some level of a plan in place (Figure 53.1).

In terms of focus, two categories bubble to the top:

- **Individual health**

  Three-quarters of the companies surveyed provide employees with health and wellness consultations, and 60% offer smoking cessation programs and incentives. Fitness incentives aren't far behind with 44% of respondents placing fitness facilities onsite or reimbursing employees' gym memberships (Figure 53.2).

- **Workplace environment**

  In an industry that has traditionally focused on process design over work environment, it's refreshing to see that 75% have incorporated daylighting technology into the workplace (Figure 53.2). And, perhaps taking the lead from the experience of tech companies, just over half now offer open space like walking or biking paths onsite.

75%

of respondents have incorporated daylighting technology into the workplace

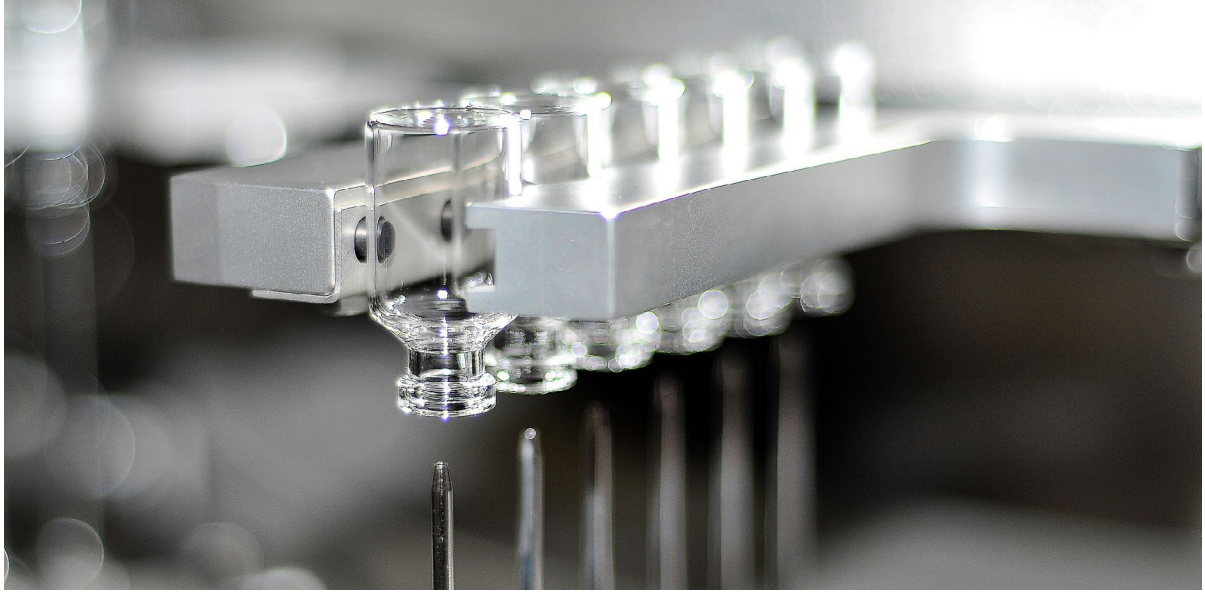
With the pandemic disrupting workplaces, particularly those with office-based teams, enticing employees back from work-at-home desks will be a challenge. These initiatives have been shown to improve employee productivity, and they also play a role in attracting and keeping talent. Many prospective employees will prioritize a company's values and actions in ESG when looking for employment. And not just for their own benefit, but to the greater good as well. In fact, 88% of millennials want to work for a company whose values reflect their own.

It's safe to say that the work environment and wellness amenities have never been so meaningful, and we expect this trend to continue upward.

PROFIT

There remains a perception that sustainability is a cost, rather than a potential contribution to the bottom line. And while specific technologies may still have a relatively long ROI, this thinking is starting to shift. According to McKinsey & Company, "ESG-oriented investing has experienced a meteoric rise. Global sustainable investment now tops $30 trillion—up 68 percent since 2014 and tenfold since 2004."

Companies need to consider the opportunity cost of resisting ESG initiatives. The question is: can you afford not to?



As we mentioned earlier, the regulatory environment is going in one direction: green. Incentives will transition into code, and companies will need to be ready. The survey revealed a perception that sustainability upgrades will disrupt operations and slow progress, with 40% listing this as a key challenge (Figure 51). This is no longer the case. In our experience, projects can reduce their impact and accelerate their schedule by leveraging Prefabrication, Preassembly, Modularization, and Offsite Fabrication (PPMOF) without affecting current operations.

40%

of respondents listed sustainability upgrades disrupting operations as a key challenge

Interestingly, 44% of companies report including supply / value chain in their carbon footprint metrics (Figure 54). They're relying on suppliers to help them fulfil ESG goals, and increasingly, to show employees and customers what they value. Is your firm losing out on potential ESG savings without supply chain policies in place? What's more, can you provide evidence of your own practices if they are required of your customers?

Conclusion

Life sciences companies see the importance of sustainability strategies, but many continue to underfund these initiatives. However, we expect to see priorities continue to shift, and the curve on adoption rise. The reality is that customers, employees, and shareholders are starting to demand it. What's more, as companies re-shape perceptions around ESG, company value and profitability, they'll start to see that this is no longer a cost, but an opportunity to attract investment and improve the bottom line. And so, the real question is not whether to allocate funds, but rather, can you afford not to?

The Role of Culture in Coping With Change:
A conversation with Jim Breen

Jim Breen, PE, LEED AP, is the Vice President, Lead Biologics Expansion at Johnson & Johnson. Over the last 20 years, he has held multiple roles within J&J, including engineering, project management, and network management based in Asia, Europe and the United States. He is a proponent of technological and digital innovation to streamline processes and improve patient outcomes.

We created our Horizons survey to understand how pharmaceutical innovators are responding to today's climate of uncertainty and rapid transformation, and to predict where the industry will go next.

Here, we add specificity to that broad picture by taking a deep dive inside one survey respondent's answers. Meet Jim Breen, whose 25 years with Johnson & Johnson have shaped his views on innovation, digitalization, and why your own company's culture may be its greatest asset.

CRB:
Many people from pharma start-ups responded to our survey. What's your best piece of advice for those at the beginning of their drug manufacturing journey?

JIM BREEN:
You might expect me to talk about advanced technologies or a certain commercial strategy here, but my answer is actually quite simple: the best way you can prepare your start-up for future growth is by focusing on your culture.

To navigate change and to adapt and thrive when things get tough, a strong company culture is key. During the pandemic, for example, companies shifted overnight from face-to-face interactions to a virtual workplace. If you enter a situation like that with a well-established culture of trust and accountability in place, you're far better positioned to make the necessary adjustments without losing momentum.

You don't get a strong culture by wanting one. You get it by defining your values clearly and by living them every day, at every level of your company.

-Jim Breen

I saw this play out at J&J in a big way. I went from spending nearly 70% of my time on the road to working almost entirely from home, as did my colleagues. Many of us had children at home or other complicated logistics to juggle. The distance between our personal and professional lives shrank, which could have led to breakdowns in trust and communication. Instead, we fell back on transparency, empathy, and mutual respect—not because we suddenly had to, but because these values were already part of our company culture.

The thing is, you don't get a strong culture by wanting one. You get it by defining your values clearly and by living them every day, at every level of your company. In our case, those values are codified in our credo, written by Robert Wood Johnson in 1943. He knew that his company would need a moral compass to succeed in a world of constant innovation, so he made one.

That credo still exists nearly eighty years later, not because it's written down but because we're in the practice of living it every day, pandemic or not, from the C-suite all the way to the lab bench. I believe it's just as important for start-ups to get this aspect of their company figured out as it is to get the right funding, or the right talent, or the right technology. It may even be the most important thing to get right.

CRB:
If culture is so important at the company level, what about for the industry as a whole? What role has culture played in the life sciences sector over the last year and a half?

JIM BREEN:
Partnership has always been part of the pharma industry's culture as a whole, and J&J's strategy in particular, but the compelling need for a COVID-19 vaccine intensified our use of collaboration. The industry's biggest leaders immediately got to work building or expanding strategic partnerships with contract manufacturers and regulatory bodies around the world, creating a level of productive partnership that we've never quite seen before.

Collaboration also took off between the executive layer of pharmaceutical operations and those working on the front lines. CEOs and other company leaders took it upon themselves to understand complex supply chain dynamics, to seek out critical information, and to get involved in removing barriers and solving for market shortages and other constraints. That's how our industry reduced a typical four- or five-year vaccine development lifecycle to just twelve months: through collaboration at every level.

SURVEY SPOTLIGHT

Pre-COVID-19, what were your most significant business drivers?
1=Most important, 4=Least important

	Most important
Overall cost of goods for product	1
Cost of product	2
Cost of project	3
Speed-to-market	4
	Least important

Post-COVID-19, what are your most significant business drivers?

	Most important
Speed-to-market	1
Overall cost of goods for product	2
Cost of product	3
Cost of project	4
	Least important

Source: CRB

Now the question is, how much of that is going to stick? The world has seen how fast this industry can move when there's a critical need, and companies will leverage all that we've learned over the last year and a half to accelerate their drug development pipelines going forward. That's why I consider speed-to-market a top business driver, post-pandemic; first-movers have the advantage of setting a standard that everyone else has to meet.

But speed doesn't come for free. It requires a certain level of risk tolerance. And for it to pay off, you need other critical elements in place. You need a sustainable cost of goods. You need trusted partners. And you need assets that are harder to measure, like a commitment to flexibility.

CRB:
Flexibility is a hot topic lately. Why is that?

JIM BREEN:
Because it's absolutely essential for today's life science companies. That's true whether you have a global manufacturing footprint or you're a newly minted start-up. Revolutionary changes to how a drug is made, and what patients expect from it, are coming faster than ever, and you can't know for certain how these changes will impact your product pipeline in the next few years. The only way to keep up is to design flexibility into your company at a strategy level, a systems level, and a facilities level.

Manufacturers are building the airplane while flying it. We have to prepare for all-new technologies and design extremely flexible facilities that look nothing like yesterday's single-product plants—facilities that can adapt as rapidly as the world around them.

-Jim Breen

Take the concept of personalized medicine. For the first time, drug innovators are able to cure certain cancers and other diseases by engineering individual cell and gene therapies. This breakthrough will alter pharmaceutical manufacturing forever. Instead of churning out a single product by the millions, we're talking about small batches of complex, patient-specific therapies. That's where the future of medicine is going, and we need to be ready. But, in the time it takes to design and build a new facility, our understanding of these therapies will evolve significantly, and so will the processes and technologies needed to make them.

What this means is that manufacturers are building the airplane while flying it. We have to prepare for all-new technologies and design extremely flexible facilities that look nothing like yesterday's single-product plants—facilities that can adapt as rapidly as the world around them.

You don't have to be a cell and gene therapy innovator to need flexibility, though. What if there's a spike in demand for your blockbuster product, but patients want it in a pre-filled syringe for at-home administration and your plant only fills vials? This is a real-world scenario, by the way, triggered by the public's wish to avoid unnecessary interactions with the healthcare system during the pandemic. If you plan for flexibility by investing in production lines capable of filling vials, syringes, and cartridges simultaneously, this kind of unexpected shift in the marketplace isn't a risk. It's a competitive advantage.

At J&J, we maintain flexibility in part through our hybrid in-house/CDMO manufacturing strategy, which gives us the versatility and the scalable capacity to accommodate changes to our product portfolio. We've also looked at our internal model through the lens of flexibility. The way we're using data and technology together is changing, and we need to make sure our people are ready. That means upskilling current operators, recruiting new talent, and building bridges between those who know data and those who know manufacturing.

SURVEY SPOTLIGHT

Do your product plans envision in-house production or the use of a contract development and manufacturing organization (CDMO)?

- ○ In-house
- ○ CMO/CDMO
- ◉ Combination of in-house and CMO/CDMO
- ○ Licensing/partnerships

Source: CRB

CRB:
Speaking of new technologies, in our survey you shared that many Johnson & Johnson facilities are at Level 4 in the Digital Plant Maturity Model. How important is digitalization to your overall business strategy?

JIM BREEN:
As I speak with you, I'm sitting in one of our most advanced plants, located in Cork, Ireland. The way we leveraged automation and artificial intelligence to connect this plant's R&D and manufacturing pipeline earned us a spot in the World Economic Forum's Global Lighthouse Network, which is a prestigious accomplishment for us.

This plant shows what today's technologies can do to improve reliability and drive efficiencies in drug manufacturing, but it's just one of many plants that we operate around the world. For those other existing sites, we face a question much like the one you're asking me now: Will our investment in digitalization pay off?

SURVEY SPOTLIGHT

Using the five levels of the Digital Plant Maturity Model, what level most accurately describes your company?

- ○ L1: Pre-digital with paper-based process
- ○ L2: Digital islands, with non-integrated pockets of automation
- ○ L3: Connected facilities, incorporating some automation and integration
- ● L4: Digital and integrated facilities, with predictive, real-time analytics
- ○ L5: Fully adapted facilities, with autonomous, self-optimizing and plug-and-play operations

Source: CRB

In the recent past, answering that question might have been more difficult. But today's smart technologies have matured to the point that they are not only important to our business strategy—they're mission critical.

Consider the fact that, traditionally, drug manufacturers factor a certain volume of product loss into their throughput calculations. That's because operators can only recognize an out-of-spec issue once it happens, which often means throwing out the whole batch. Take that loss and multiply it over weeks, months, or years of operation, and it becomes financially significant.

Now imagine integrating a predictive manufacturing system guided by artificial intelligence. That system can run multivariate analyses in real time, anticipate problems before they happen, and automatically make the necessary adjustments to your instrumentation. As a result, you're no longer writing off lost batches. Your capacity has increased significantly. You've taken huge costs out of the system, which more than offsets your upfront investment in advanced digital technologies.

When it comes to digitalization, it's easy to get caught up in the buzz and much harder to stay grounded in the business case.

-Jim Breen

The fact is, those savings are just the beginning. You're also reducing human error by introducing reliable, repeatable automation to the plant floor, which means less rework and greater reliability in your throughput. In fact, advanced automation will soon make it possible to run 'lights-out' pharmaceutical plants. That means far less labor and less energy required—good news from both a business and an environmental perspective.

I'm excited to see where these advances take us next, although I will warn your readers to study the difference between technologies that deliver a real payback and those that simply look cool. This is top of mind for us at J&J as we ready ourselves to take our digital maturity even further. When it comes to digitalization, it's easy to get caught up in the buzz and much harder to stay grounded in the business case. Do your due diligence, and your investment will pay off.

CRB:
From your survey responses, it sounds like J&J is as ambitious about sustainability as it is about digitalization.

JIM BREEN:
Nobody was talking about sustainability back in 1943 when Robert Wood Johnson wrote our credo, and yet that document says clearly that protecting the environment and its natural resources is part of our moral responsibility as a company.

Putting that responsibility into action starts at the corporate level. In the early 2000s, our leadership team promised that every new Johnson & Johnson construction project would be LEED certified. The LEED program was less than ten years old at that time, and we were one of the first companies to embrace it so fully.

SURVEY SPOTLIGHT

Does your company have formalized sustainability metrics or benchmarks that it is measuring against?

- (●) Yes, we have concrete, defined goals
- ( ) Yes, but we have not developed metrics for measuring progress
- ( ) Not yet, but we are developing goals
- ( ) No, have no plans

Source: CRB

This is the type of commitment that trickles down into all other levels of the company, influencing our entire workforce to aspire toward sustainable practices. But influence can only go so far. If you're a plant manager and you have the capital funding to add a new manufacturing capability or to reduce your energy load with some new technology, chances are you're going with the new capability. Our leaders realized that to empower people within the company to meet our sustainability targets, we'd have to put money where our credo was.

SURVEY SPOTLIGHT

To what level is your company's sustainability plan affecting operations?

- Corporate level
- Site level
- Project level
- Individual level

Source: CRB

That's why we came up with the "capital relief fund." If one of our employees has an idea related to sustainability, and if they can demonstrate that their idea will both reduce the environmental impact of an existing plant and net a positive financial return over time, then this fund is available to help them make that idea a reality.

This goes full circle back to my point about company culture. It doesn't just mean that your employees like working there. It doesn't just make good business sense. It doesn't just help drive sustainability and responsible stewardship. A strong culture does all of those things and more. I truly believe that it is the key not only to supporting each other through this current pandemic situation, but to building a world in which we all thrive—as individuals, as an industry, and as a connected, global community.

AUTHORS

Noel Maestre, PE, LEED AP, is the Vice President of Life Sciences focusing on strategy and evaluating market trends for CRB's global life sciences practice. He has an extensive background in mechanical and process utilities engineering, specializing in design, construction, and start-up of biotechnology, pharmaceutical, and advanced technology facilities.

Peter Walters is the Director of Advanced Therapies at CRB with 20 years of experience specializing in pharmaceutical process and facility design. He has a deep technical background designing equipment and processes for multi-process facilities predicated on maximum flexibility, logistics optimization, and technologies that reduce costs while allowing pipeline expandability and higher quality therapeutics.

Bill Jarvis is a Senior Process Engineer and Specialist in oligonucleotide facility design, with more than 45 years experience in process engineering of peptide, small molecule API, high potency API, active drug conjugates, containment facilities and aseptic processing facilities and equipment. He's held various roles within related ISPE communities of practice.

Jim Love is the market leader for Oligonucleotides at CRB, focusing on strategy, market trends, and operational best practices. He is a consultant and project leader for strategic business case studies for the pharmaceutical and biotechnology industries and has extensive industry experience including design engineering, manufacturing operations, and product launch.

Brendan Nichols is a Process Engineer specializing in oligonucleotide facility design. He has an extensive background delivering solutions to oligonucleotide clients on projects of varying scale. Brendan's technical background also includes process engineering of peptide, small molecule API, and cell culture facilities.

David Estapé, a long-time biotechnology expert who holds a doctorate in chemical engineering and has 22 years of experience. He has worked on major biotech projects globally, driven biotech strategy internally and participated heavily in organizations like the International Society for Pharmaceutical Engineering, BioPhorum Operations Group and Parenteral Drug Association.

Ken Jacobson is the Chief Process Engineer with deep experience with biotechnology, pharmaceutical, environmental and chemical processes. His work includes conceptual and detailed process design, qualification, start-up, operation and facility optimization. He was a co-author of the process equipment chapter for the ISPE/FDA Baseline Guide for Design of Biopharmaceutical Facilities

Can Aktar is an established and proven technical operations and project management professional with multi-national and multi-disciplinary experience. His experience spans the complete life cycle of biotechnology operations and project development. He is an ISPE Certified Pharmaceutical Industry Professional (CPIP).

Jake Adams is the RNA Therapies market leader at CRB, focusing on market strategy and execution of projects in these developing therapeutic fields. The combination of his engineering background and project management skill set allows him to bring innovative and right-sized solutions to clients.

Yvonne Duckworth, is a Senior Automation Engineer with over 30 years of pharmaceutical industry experience. She has extensive background as a Pharma 4.0™ SME providing Digitalization consulting and roadmap implementation for Pharma clients. She is a Co-Chair of the ISPE Pharma 4.0™ Special Interest Group and is a committee member and frequent presenter at multiple industry events.

Niranjan Kulkarni, PhD, is Director of Operations Improvement at CRB, specializing in data modeling operations and process simulations, layout optimizations, and supply chain management. He has worked with pharmaceutical, biotech, food, chemical, semiconductor, electronics assembly, and packaging industries.

Matt Edwards is the Director of Digital Delivery, leading a team of virtual design and construction professionals across CRB's global offices. Matt is passionate about Construction 4.0 and how a combination of innovation, data, and digital tools is transforming the future of the architecture, engineering, and construction industry.

Dominic Tate is a construction project manager with recent experience delivering COVID-19-related projects at warp speed—70% faster than typical benchmarks. He has 10 years of experience in the construction industry with a focus on biotechnology, pharmaceutical, and high-technology laboratories and manufacturing facilities.

Christa Myers is the Aseptic and Sterile Products Market Leader for CRB. She has directed multiple directives to support excellence in design, execution, and delivery of projects. Her leadership drives innovation responsibly into projects and operations. She is a recognized Author of the ISPE Sterile Products Processing Baseline Guide and is the Co-Chair of the ISPE Aseptic Conference.

Jarrod Wrampe is a Market Team Leader with over 20 years of experience. While Jarrod is an SME in critical utilities, he functions as many clients' single point of contact as Project Executive for many strategic pursuits. Jarrod leverages his broad facility engineering and construction knowledge to bring projects to life.

Mike Barrett is the Vice President of Project Delivery Services and a champion for Lean execution methods. He has vast project experience including over 200 life science projects totaling nearly $1 billion. Mike is passionate about building collaborative, focused teams that have deep levels of trust, all working toward a common project purpose.

Carl Rohs has more than 30 years of experience building life sciences facilities and focusing on the continuous improvement of project execution. He is skilled at implementing lean practices on capital projects, and building a strong culture of trust and commitment with his project teams.

JP Bornholdt is the Director of SlateXpace Operations at CRB, working with project teams to apply innovative approaches such as flexible design strategies, scalable turn-key technologies, modular, offsite fabricated, and integrated project deliveries. A licensed architect and engineer, his multi-discipline expertise provides a strong basis for integrated facility design and construction.

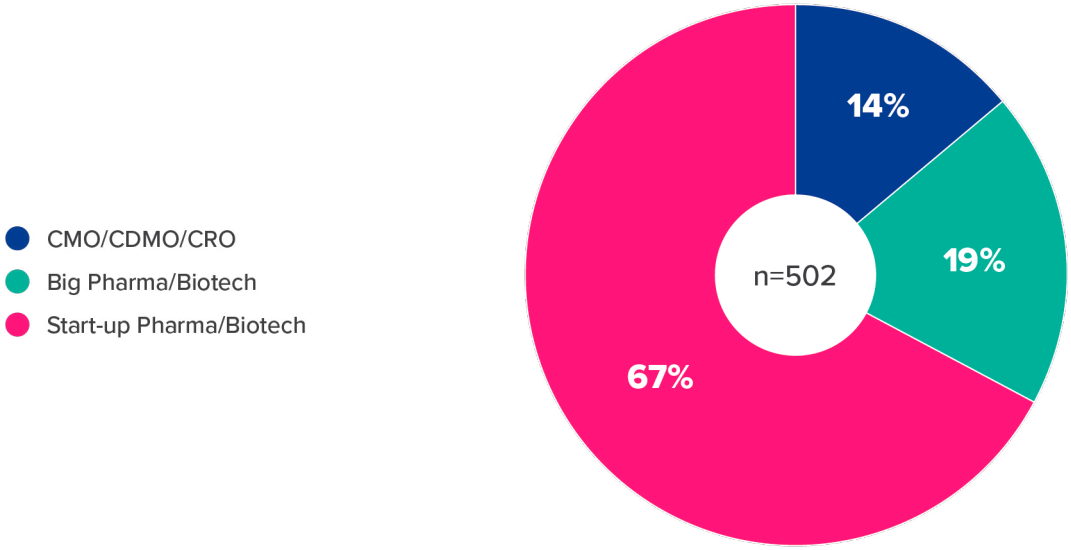
Dennis Kearney is a Senior Project Manager and subject matter expert in prefabrication, preassembly, modular, offsite fabrication (PPMOF). Over the last 30 years, Dennis has managed all aspects of capital projects from concept through start-up for biotechnology and pharmaceutical clients.

Jeff Wegner is a registered mechanical engineer, Certified Energy Manager and LEED Accredited Professional with experience in mechanical design and project management. He is passionate about innovative and sustainable projects that have a meaningful impact on energy consumption and affect the clients' bottom line.

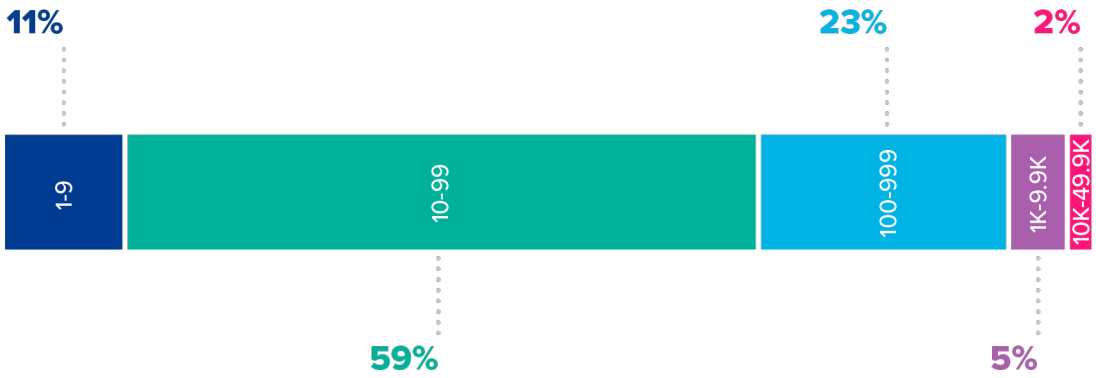
Maya DeHart, LEED GA, is a process engineer with experience managing process design from concept through construction. As an accredited Leadership in Energy and Environmental Design (LEED) General Associate, Maya has lead the establishment and execution of sustainability goals on capital projects across the life sciences industry.

FIRMOGRAPHICS

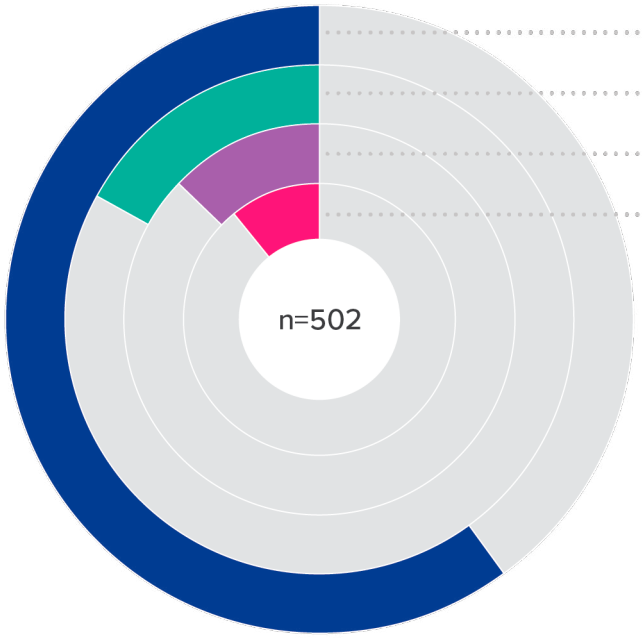
Company Type



Number of Employees in Company



Primary Sector



60% Pharma/Biotech

17% Pharma/Biotech, with biotech focus

13% Pharma/Biotech, with pharma focus

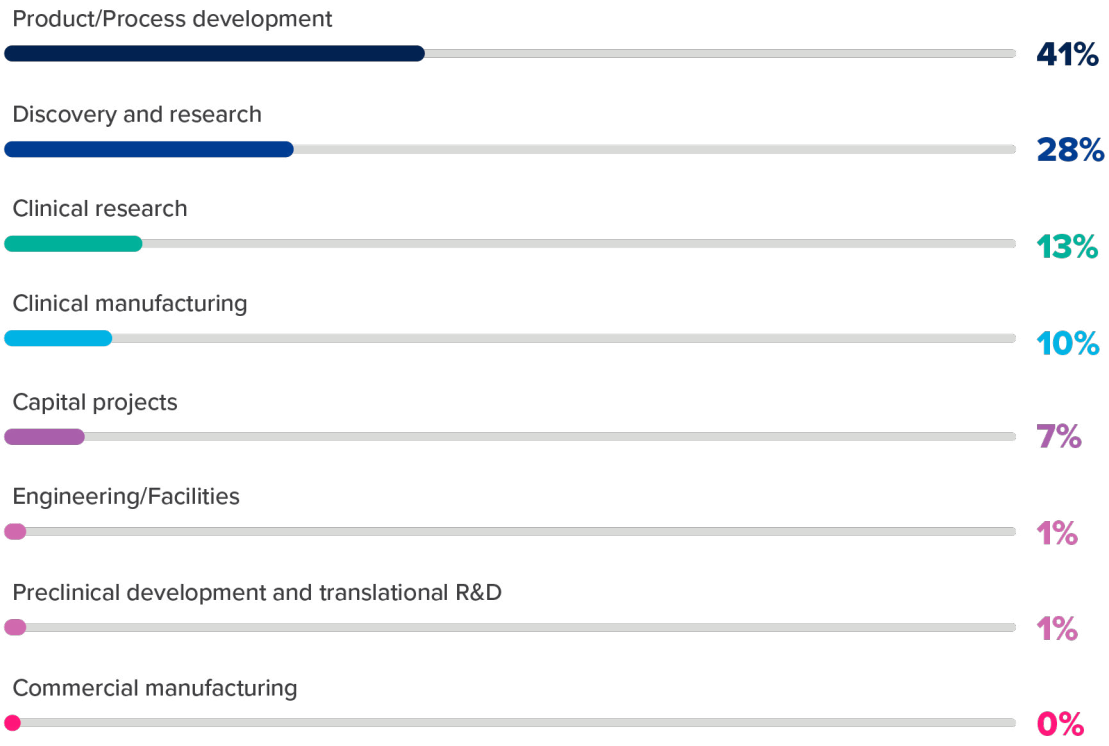
11% Pharma/Biotech, with cell and gene therapy focus

Primary Role

Area of Focus

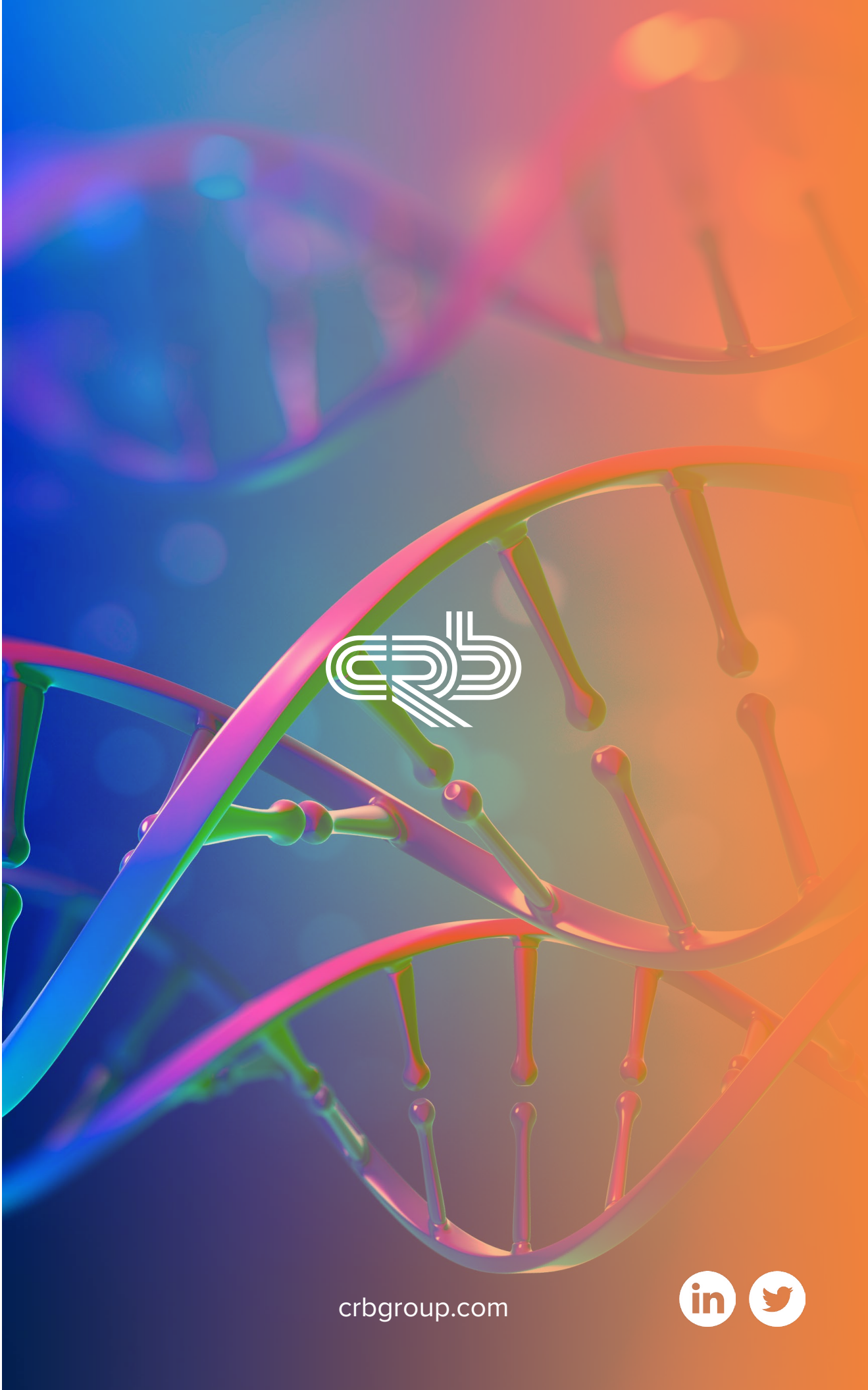
Primary Target Market

Primary Job Function



Legal Notice

The information contained herein is of a general nature and is not intended to address the circumstances of any particular individual or entity. Although CRB endeavors to provide accurate and timely information, there is no guarantee that such information is accurate as of the date it is received or that it will continue to be accurate in the future. No one should act upon such information without appropriate professional advice after a thorough examination of the particular situation.



crbgroup.com