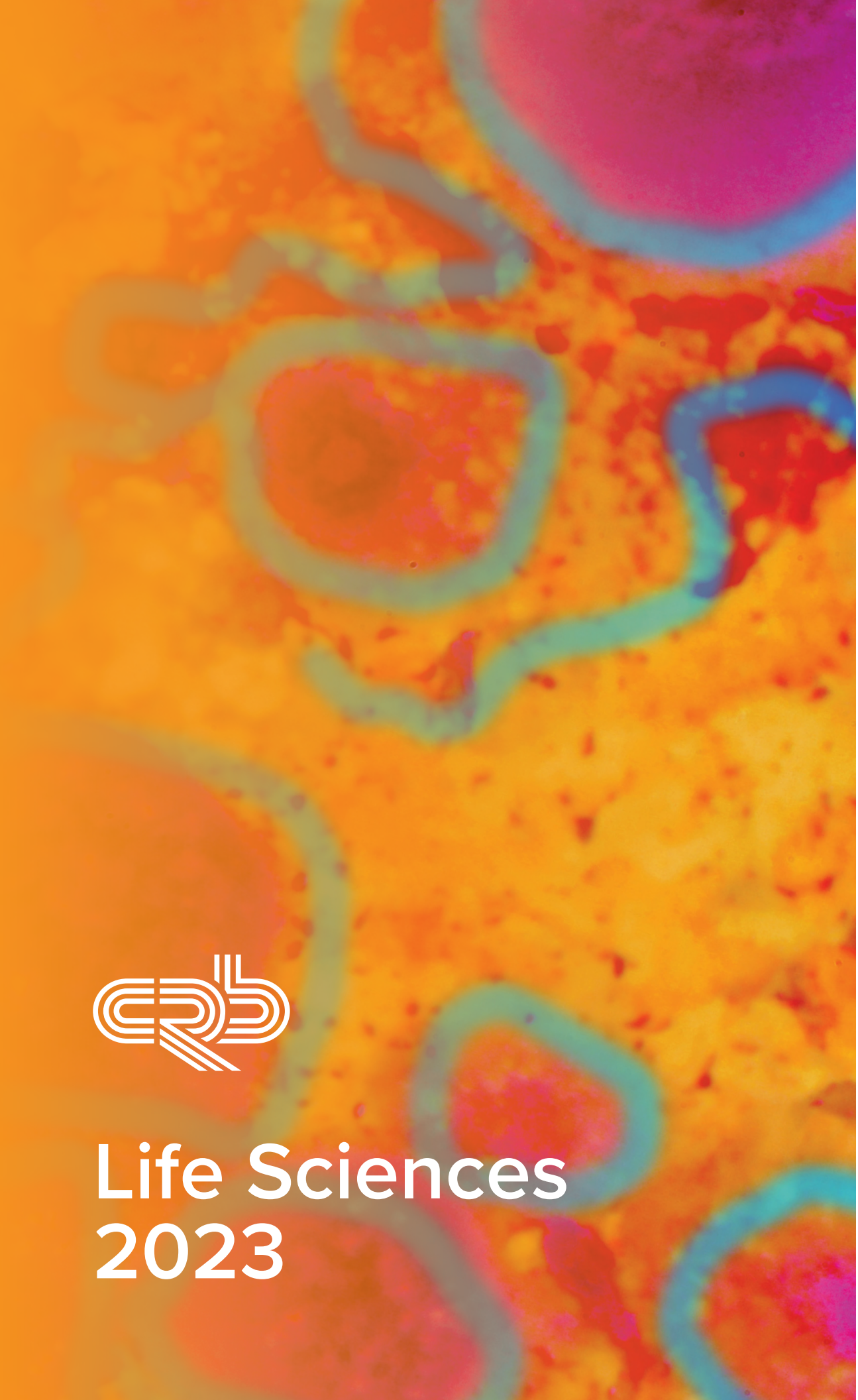


Life Sciences 2023

HORIZONS

About this Report

In 2020, CRB introduced its first *Horizons* report focused on life sciences. Deep into the COVID-19 pandemic, it was an incredibly timely way to examine the manufacturing challenges of getting critical treatments to patients. Moving therapies and vaccines from R&D to commercial-scale production has never been easy, and somehow COVID-19 managed to put a warp-speed clock on it all.

Three years later, focus remains on the question of access: How can manufacturers improve the pathways to pioneering therapies? As Noel Maestre, CRB's Vice President of Life Sciences, notes in the report's opening summary, "Unfortunately, the distance between an emerging therapy with regulatory approval and mainstream access for the patients who need it remains wide in many cases."

That challenge is among many examined in this fourth *Horizons: Life Sciences* entry. This year's report is built on the survey responses of more than 500 leaders from small, medium, and large companies across North America and Europe. Our experts go deep on a variety of sub-markets, writing prescriptively about where the industry is today, and where it's headed.

The result is another exhaustive analysis of manufacturing trends shaping everything from RNA and cell and gene therapies to anti-body drug conjugates. We also explore the revolution promised by Industry 4.0, and how readily our industry is embracing digitalization and data to speed therapies to patients.

We're proud to bring you this report, and we invite your own reflections about how our industry can move forward. Submit your feedback through our contact page at crbgroup.com, and we wish you a safe and prosperous 2023.

Sam Kitchell
Chief Operating Officer, CRB

The price of life-saving innovation:

Today's life science industry is giving patients hope. Can it give them access, too?

By: Noel Maestre

Executive Summary

At a time when the life science industry is producing one first-in-class therapy after another, allow me to make what I'm sure is a first-in-class statement: *Jurassic Park* has something to teach us about life-saving medicine.

Sure, there's the obvious bit where an animated double-helix explains dino DNA. Now thirty years old, that scene still holds up—in fact, we could find ourselves once more sharing this planet with the woolly mammoth, thanks to the landmark de-extinction research underway at Colossal Laboratories & Biosciences. There may not be fossilized mosquitos involved (sorry, Mr. DNA Sequence), but today's scientific advances are making *Jurassic Park's* impossible premise more possible every day.

That's not the scene I'm thinking of, though. No, I want to draw your attention to a moment later in the film, when John Hammond, the man behind the movie's infamous attraction, wags his finger and says: "This park was not built to cater only for the super rich. Everyone in the world has the right to enjoy these animals."

Think about that. Think about the debate currently underway across the life science industry—a debate that weighs the cost of bringing a new drug to market against the resources available to patients who need it and funding systems that pay for it. No innovator develops products only for the super rich, but until researchers, manufacturers, regulators and insurers coordinate their efforts to move scientific breakthroughs into the mainstream marketplace, that may be the future—which is even more grim than the destiny awaiting John Hammond's park.

Fortunately, the number of emerging drugs targeting rare diseases and the evolution of simplified platforms is bringing our industry closer to a more accessible future for patients. And although big-name companies like Takeda have recently pulled back from select emerging markets, technology platforms or peripheral therapeutic areas, tenacious pioneers are sticking around, leveraging new technologies to accelerate development and improve access pathways.

This report, the fourth in our *Horizons: Life Sciences* series, tests this vision of improved patient access. We draw on the perspective of more than 500 small, medium and large companies operating across North America and Europe to examine each submarket in detail, looking closely at the milestones that brought them to this moment and the trends that are shaping their future—trends that will determine how quickly the next revolution in life-changing medicine will unfold.

1. CLIENT SPOTLIGHT: PATIENTS AS PARTNERS

Meet Max Moore, Vice President of Manufacturing and Operations at Ionis Pharmaceuticals. Ionis is part of a growing movement of life science companies that are finding new and meaningful ways to "walk the walk" of patient-focused pipeline development. In this article, find out how Max and his team stay focused on impact-driven drug discovery by working directly with patients, their families and the organizations who advocate for them—and what it means to develop a culture of vulnerability, tenacity and transparency inside a pioneering drug company.

2. AN OVERALL PERSPECTIVE ON THE LIFE SCIENCE INDUSTRY

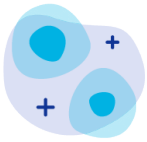
With less money flowing into the life science industry since the boom of two years ago, are manufacturers taking a step back? Or are they using this slowdown as an opportunity to prepare for future growth?

That's the question driving Peter Walters and me as we follow the survey data deep into this industry's current landscape. We discovered a feeling of cautious optimism among today's manufacturers, who are doubling down on R&D with the help of AI-powered technologies while approaching their CGMP programs with a conservative and grounded frame of mind. Meanwhile, an increasingly progressive regulatory environment and a healthy marketplace of contracted services is helping them get ahead—and get more life-saving therapies to the patients who need them.

3. CODING RNA TECHNOLOGIES

The success of mRNA vaccines opened the door for all coding RNA technologies. In this article, Steve Attig and David Estapé home in on responses from those making coding RNA drug products, specifically therapeutic and/or prophylactic vaccines, and find continued enthusiasm for mRNA as a modality.

While almost all of the mRNA experts pointed to the potential of mRNA for therapeutic vaccines, vaccine developers continue to embrace coding RNA to prevent infectious diseases. Despite these high expectations for the development and production of therapeutic vaccines, significant differences exist between those in North America and Europe. Sure, there are challenges—product safety and the need for more patient data chief among them—but these are solvable, as suggested by the innovative technologies and trends our survey respondents believe will release the therapeutic and commercial potential of these novel drugs.



4. CELL THERAPIES

Of the 500+ life science companies represented in our survey data, more than three in four have a cell therapy product in their pipeline. This submarket, once the focus of boutique researchers, is clearly a mainstay of the industry, with innovation happening everywhere from small startup labs to the research centers of "big pharma." As a result, breakthrough discoveries and first-in-class regulatory approvals have become regular events, with the potential to impact countless patients and their families.

Join specialist Michela Castellani-Kleinschroth, based in CRB's Basel office, inside this zeitgeist. With the survey data as her lens, she examines the biggest challenges facing today's cell therapy manufacturers, from commercialization to decentralization, and the role that emerging gene editing technologies could play in getting more therapies to the patients who need them, more quickly.

5. GENE THERAPIES

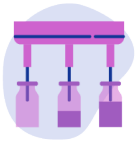
Life science innovators with gene therapies in their pipeline appear to belong in one of three camps. Some are pulling back. Others are focused on bringing their viral-based products to market, and they're investing in stable producer cell lines to help them get there—whether that means developing their own or licensing a third party's technology. And then there's a third group that has its sights set on emerging non-viral manufacturing methods to move them from the research bench to the bedside.

In this article, Peter Walters examines these dynamics in context with our survey data, giving an insider's perspective on the push-and-pull of scientific discovery and commercial feasibility—and on how this push-and-pull impacts not only manufacturers, but also the contractors who support them and the patients who depend on their success.

6. ANTIBODY-DRUG CONJUGATES

The growing number of approved antibody-drug conjugates (ADCs) on the market, as well as the hundreds of ongoing clinical trials, has shown that these drugs are taking their place alongside other exciting developments in the life sciences.

However, companies need to address the unique difficulties of manufacturing these highly toxic drugs. In this piece, Ashley Harp analyzes what ADC developers and manufacturers are doing right now and how they're planning for the near future to meet these challenges. Companies of all sizes are concerned about the production of liquid and solid waste, particularly the large volumes of solvents typically needed. Fortunately, the emergence and uptake of new purification technologies—like continuous chromatography—promise to reduce solvent use and, at the same time, accelerate the rate of production. Additionally, as the cytotoxicity of these targeted therapeutics continues to increase yearly, industry experts recognize the need for enhanced safety.



7. DRUG PRODUCT MANUFACTURING

Without exception, and regardless of product type, aseptic and sterile product facilities ensure that patients receive safe life-saving therapies. The constant pace of innovation in drug development filters down to the design of these facilities, the equipment and packaging they use, and how they are regulated. In this piece, Luke Stockhausen explores the impact of the recent EudraLex Annex 1 deadline on respondents from European- and North American-based companies.

Armed with the knowledge that new regulations can only be truly understood once they are stress-tested by inspectors, the European cohort is taking a cautious approach. They seem to predict that more time and resources will be required to fully comply with the new regulations. What's more, they appear to be holding off on developing new technologies until they see how Annex 1 plays out. Watch this space—we have a year of learning ahead.

8. DIGITALIZATION

While the life science industry lags far behind retail, banking and the automotive industry in terms of using data and AI, we learned in last year's *Horizons* report that companies were rapidly pushing Industry 4.0 initiatives.

This year's survey suggests that this maturation curve is continuing. As Ryan Thompson and Niranjan Kulkarni found that when industry experts were asked about their use of data and AI, almost everyone is on their way to using the manufacturing and quality data they're collecting,

and most intend to be using AI tools within two years. They have the budgets to support their digital strategies, a skilled workforce in place and C-suite executives taking ownership of digital transformations, making these updates more likely to occur. Despite considerable skepticism that investments in digitalization will be rewarded, the overall impression is of an industry finding its way into a digital future.

What's next?

Thanks to the innovation underway in today's R&D laboratories, there may be hope for the woolly mammoth—and there most certainly is hope for patients who, until now, had no way to conquer a life-threatening condition.

However, the distance between an emerging therapy with regulatory approval and mainstream access for the patients who need it remains wide in many cases. For that to change, funding systems designed to support ongoing treatment need to prepare for a future of one-time curative therapies. Researchers and manufacturers, meanwhile, need to keep doing what they're known for—developing novel tools and strategies to accelerate and streamline the process of bringing new drugs to market.

This report highlights the most impactful of those tools and strategies, giving today's innovators a perspective on tomorrow's opportunities—and a reason to continue sprinting for that horizon.

Developing a patient-centered pipeline

A conversation with Max Moore, Vice President, Manufacturing and Operations, Ionis Pharmaceuticals

Section 1

If you were part of the Ionis team, you would have logged into your inbox on a recent Wednesday morning to find a company-wide email that began, “In case you forgot why you came to work today.”

That internal email, which came from Max Moore, VP of Manufacturing and Operations, describes promising data from a Phase II study of Spinraza®, a first-in-class antisense oligonucleotide therapy developed by Ionis and Biogen to treat spinal muscular atrophy (SMA) (Biogen licensed the global rights to develop, manufacture and commercialize Spinraza from Ionis). After five years, newborns who had received Spinraza while presymptomatic had gone on to achieve their motor milestones—a major leap forward for pediatric patients facing this disease.

The implications of Max’s email are clear. Like a growing portion of the 500+ life science innovators who participated in this year’s *Horizons: Life Sciences report*, Ionis is working hard to walk the walk of their patient-focused mission. Through direct and ongoing engagement with patients, their families and the advocacy groups who support them, the Ionis team has developed a robust pipeline of RNA-targeted therapeutics for a host of underserved patient populations—and behind that pipeline, they’ve nurtured a company culture that’s focused on the humanity of drug discovery, and how best to harness the science of antisense medicine as a vehicle of hope for those who need it most.

Ionis: a Snapshot

- *Strong R&D focus on early development of antisense drugs, now transitioning into a fully integrated manufacturing company with a commercialization engine*
- *More than 40 active programs in development*
- *Four approved drugs and eight late-stage pipeline medicines for 10 indications*
- *850+ employees across three global locations*

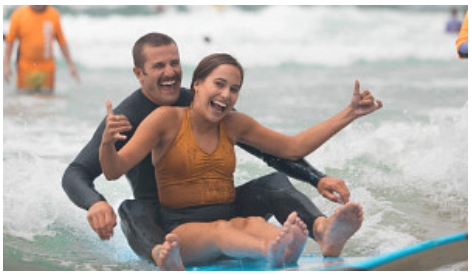
What happens behind the scenes to galvanize this patient-focused approach and ensure that it's grounded in a robust business strategy? In this article, sit down with Max Moore to find out.

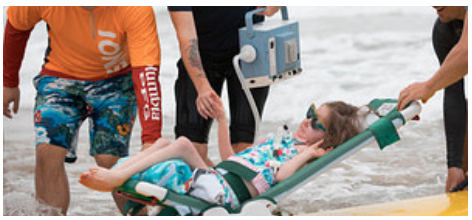
WHAT DOES IT TAKE TO TURN A MISSION STATEMENT INTO A "WAY OF BEING"?

Sick people depend on us. That concept is at the core of everything we do at Ionis. But what does it actually mean? Which sick people? What are they depending on us for? In my view, asking questions like these can turn a few simple words into a culture that permeates every part of the company.

Of course, to answer those questions, you need to ask the right people. That's why our company has developed close relationships with patient advocacy groups for each of the modalities we're pursuing. We volunteer with them, plan community events with them and invite them to speak at company-wide meetings. These opportunities for engagement help us go beyond the usual jargon to really understand the personal impact of our work.

Take the idea of a "burden of disease," for example. It's often defined as a statistic or an inventory of symptoms. That may be accurate, but it's not real. It's hard to connect to a statistic. On the other hand, when you hear directly from a patient facing profound paralysis, and





that patient explains how different his life would be if he could regain just enough movement to operate a motorized wheelchair—now that is real. That's an opportunity for connection. That's when the "burden of disease" is no longer an academic term. It's an experience reported by a living, breathing human being. A sick person who depends on us, in other words.

HOW DOES YOUR PATIENT-CENTERED APPROACH IMPACT EMPLOYEES?

Our workforce has increased by nearly 70% since 2018. As any growing company knows, it's difficult to expand that quickly while maintaining the integrity of your company's mission and culture. That's where a strong foundation matters most. From our top leadership down through every department and team in our company, we rely on a drumbeat of patient-centered thinking to keep everyone focused on their purpose.

It's easier to stick with hard problems until they're solved when you can connect the dots between the effort you invest and the potential impact of that effort. By inviting patients to the table (figuratively and literally), that's what we do: we generate stronger engagement from our employees, who see meaning in their work and feel loyal to our mission in a way that no benefits package or salary bracket could foster on its own.

Ionis saw a

70%

increase in workforce since 2018.

Also, our practice of listening to patients expands naturally into an overall "culture of listening." We have internal initiatives designed to give employees the opportunity to bring forward ideas, solutions and data-driven insights about where we might invest our time and resources next. Take our weekly Data Club, for example. Employees from across the company come together to share ideas and discuss scientific concepts in a safe, open and encouraging environment. From experiences like this, employees feel empowered to apply their best selves at work, and to motivate each other to do the same.

WHAT IS THE IMPACT OF YOUR MISSION ON YOUR APPROACH TO SELECTING CONTRACTORS?

The best contractors are those who can collaborate with you across multiple projects and for many years, which has been our fortunate experience with CRB. For companies looking to find a similar relationship, the key is to recognize a good cultural match.

That's not necessarily easy. We all know how to assess a potential partner for technical expertise, but culture—that's hard to define, and even harder to identify in the wild.

In my experience, it starts with the right environment. Technical expertise reveals itself on-site, or in a boardroom, or over a Zoom call. Cultural indicators are more likely to appear over dinner, when the conversation depends on your potential contractor's level of engagement. Are they interested in thoughtful conversation

about your project and its greater purpose? Do they ask about the patients whose lives may be impacted by the project's result? Are they curious about your hopes and dreams as a company, and do those hopes and dreams generate a passionate response from them?

By giving questions like these at least as much weight as technical questions, you'll find it easier to identify contractors who are a good fit in terms of your company's culture, mission and overall commitment to the cause. During the long, often difficult journey of project delivery, these qualities cannot be overrated—and they play an indirect but critical role in delivering the result that patients depend on.

HOW DO YOU SQUARE YOUR MISSION TO IMPACT PATIENT LIVES WITH THE COST OF DRUG DEVELOPMENT?

Costs are important. That's obvious. We all have to run cash-positive businesses in order to keep doing what we're doing for patients, and that requires a lot of honest conversations and sometimes difficult decisions about the reality of developing life-enhancing, first-in-class therapies. I can't deny that.

But I will say that it would be a mistake to put cost ahead of innovation in terms of our priorities as an industry. Look at the Human Genome Project, for example. It cost $2.7 billion—yes, with a "B"—to complete that project. If we had decided not to pursue that project because of a rational assessment of its cost, we wouldn't have the genomics industry that we've got today, and the millions of lives that are saved, enhanced or otherwise impacted by our advanced understanding of genetics would be lost. Innovation has to come first; cost can't be our only compass point.

I will also point out that innovation is the key to addressing cost considerations. As new ideas come forward, technologies improve and we develop more scalable processes to help bring emerging therapies to market faster and more efficiently, the economics of drug production will improve for developers, manufacturers and patients. Just look at consumer tech for an example: When I bought my first Apple computer, it had a tenth of the power that my current computer has, but it cost much more to purchase. The same thing happens in the life science industry, given enough time and room for innovation.

WHAT ADVICE DO YOU HAVE FOR COMPANIES THAT WANT TO DEVELOP A PATIENT-FOCUSED CULTURE?

After nearly thirty years of working in this industry, I've come to believe that companies with the greatest potential to impact patient lives share three core attributes: vulnerability, tenacity and transparency.

You've already seen an example of vulnerability in the way that our patient advocates share their experiences and needs with our team. That runs both ways: To do impactful work, our team needs to embrace vulnerability, too.

In a way, that's proof that the mission is working. To meet the needs of the sick people who depend on us, each employee makes a whole-hearted commitment,

but you can't commit your whole heart without accepting the risk that it might break once in a while. A promising compound could fail in the clinic. A trial could be halted because of poor results. If your work is centered on data and business outcomes, these curveballs are frustrating; if it's centered on impacting the lives of patients you've come to know, they become devastating.

That's where tenacity comes in. It takes endurance to keep pushing for the results that you know are possible if failure is also a possibility.

When our company began in the late 1980s, we were virtually alone. The field of antisense oligonucleotides was in its infancy. The Human Genome Project was still a year from kick-off. There was no technology platform for us to inherit as a young genomics company. Whatever we needed, we'd have to engineer for ourselves and it wasn't always a smooth journey. Sometimes we were at the crest of the wave, and sometimes we were under it. If we wanted the result of our work to reach patients, we had to learn to tolerate failure and cultivate the tenacity to keep going anyway.

> ***"Little by little, we figured out how to solve the unsolvable."***

Little by little, we figured out how to solve the unsolvable, first by developing the technology that we needed, and then by using that technology to meet the needs of patients. Today, contract manufacturing organizations and big pharma companies around the world use equipment and facility designs that we developed during this period. It took tenacity for us to come that far.

Which brings me to transparency. It's the quality that makes vulnerability and tenacity possible. During periods of difficulty, our survival as a company depended on our willingness to be honest about what was working, what wasn't and how to rebuild—if rebuilding was even the right choice. These conversations didn't happen behind closed doors. They happened out in the open, with input from across our company and our network of partners. Even more than technological knowledge, I credit our commitment to transparent and open communication for getting us where we are now, with the workforce we've built and cultivated along the way.

Today, that culture of transparency is part of everything we do. It's in the relationships we have with the patients who depend on us, as well as our relationships with each other within the company. That email that I sent yesterday about the Spinraza® trial is an example of "good news" communication, but "bad news" communication is just as important. When we face a setback, we share it, we discuss it, we make it a focal point until we can understand what happened, what the data tells us and what our next best step should be—always with the hope that we'll find the solutions patients need, while there's still time to impact their lives.

> ***"Hope is what makes us human, and at the end of the day, that's what the life science industry is all about."***

And that's what really matters: hope. I know this might sound surprising coming from me, a manufacturing and operations guy. But hope is what makes us human, and at the end of the day, that's what the life science industry is all about. Being human. Helping each other. Becoming one another's greatest source of inspiration and determination. Hope is what fuels patients as they face their greatest battles, and it's what fuels us, too, as we face the long journey from a good idea to a life-saving, in-market medicine. That's my parting advice to other companies on that journey: Put hope at the center of everything you do.

Planted, not buried:
The life science industry prepares for new growth

By: Noel Maestre and Peter Walters

Section 2

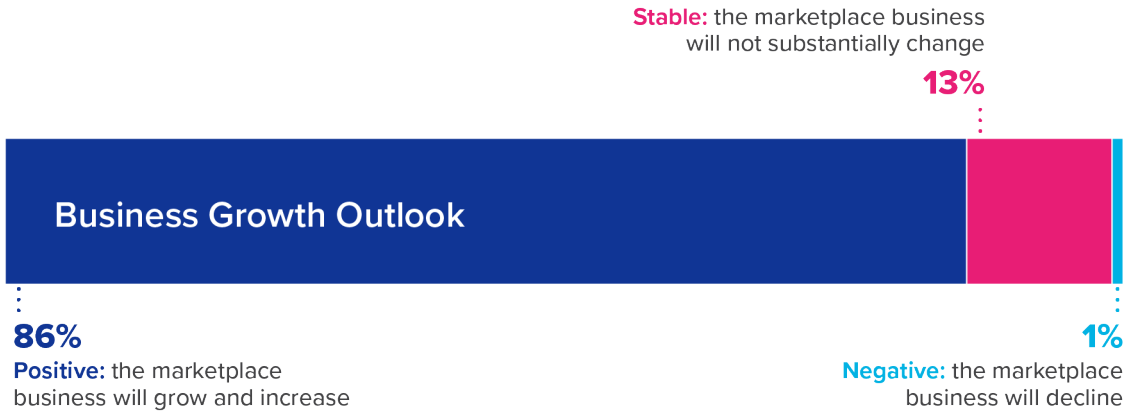
After a pandemic-fueled period of historic growth, the life science industry has found itself in a slump. Companies are making fewer deals. Financing is harder to come by. With a few exceptions for notable products on the verge of approval (particularly in the emerging cell and gene therapy submarkets), surges in innovation and discovery appear to have tapered off.

Are these dynamics forcing life science companies to pause or even roll back their plans? Or do they perceive this slowdown as an opportunity to prepare for a stronger position in the future?

The answer lies somewhere in between, according to 500+ survey respondents working on the front lines of this industry. Companies are focused on de-risking their pipeline and implementing a more calculated business approach; at the same time, they see huge potential in the industry's future (Figure 2.1).

FIGURE 2.1

In your opinion, what is the business growth outlook for the life science marketplace as a whole over the next three years?



Source: CRB

Out of this sense of cautious optimism, our survey uncovered three dominant themes that are likely to shape where the life science industry goes next—and how quickly it will get there.

1. Companies are approaching the drug development lifecycle with a grounded and focused strategy.
2. The regulatory environment is actively evolving to meet today's needs.
3. Long-term contractor relationships are an increasingly important contributor to success for life science companies.

COMPANIES ARE APPROACHING THE DRUG DEVELOPMENT LIFECYCLE WITH A GROUNDED AND FOCUSED STRATEGY

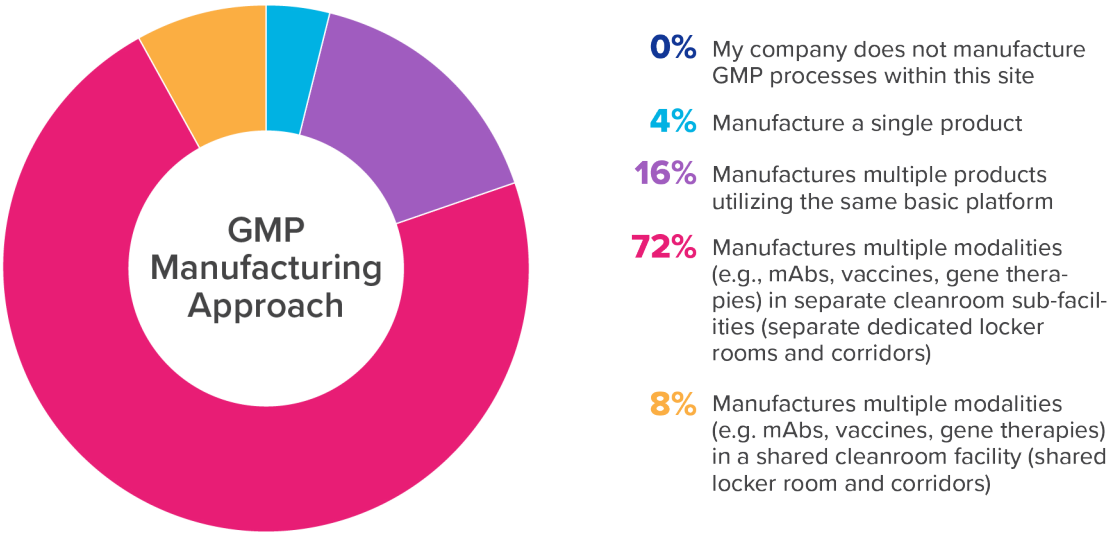
Over the last decade, we've watched the general life science industry shift away from R&D and invest heavily in CGMP operations, often with the goal of building a diverse in-house manufacturing pipeline through acquisition. Now the pendulum appears to be swinging back. Some of the industry's leading companies are divesting themselves of certain manufacturing programs to establish a narrower, more competitively advantaged pipeline. Takeda recently discontinued its programs in adeno-associated viruses (AAV) gene therapy and rare hematology, for example, citing a wish to prioritize its core therapeutics; Amicus and GSK have made similar exits.

Overcrowding in certain submarkets is part of the reason for this shift. There's also the fact that R&D isn't what it used to be, thanks to the emergence of AI-driven tools capable of machine learning and predictive analysis. In fact, when it comes to spending money on artificial intelligence, our survey respondents prioritize their R&D programs above any other (see Section 8 of this report, "Embracing data and AI"). That's because these intelligent tools make success in the research lab far more likely; discoveries that would have once taken months to manually identify and document could be possible in just weeks or days, giving companies more certainty that their R&D investment will pay off—and soon.

With all of this attention on the exciting potential of AI-driven drug discovery, companies seem to be approaching their CGMP manufacturing investment with a relatively grounded perspective (Figure 2.2).

FIGURE 2.2

What is your site's GMP manufacturing approach for producing therapies?



Source: CRB

Many survey respondents are supporting multiple modalities, and the majority are doing so by running smaller sub-facilities within a larger one, featuring segregated cleanrooms with dedicated locker rooms, corridors and support functions.

This is, of course, only a snapshot of the present moment. Already, many of CRB's clients are making investments designed to push them beyond this majority and into the top category of companies with truly multimodal facilities—a category that may include only 8% of respondents today but is likely to grow rapidly over the coming years.

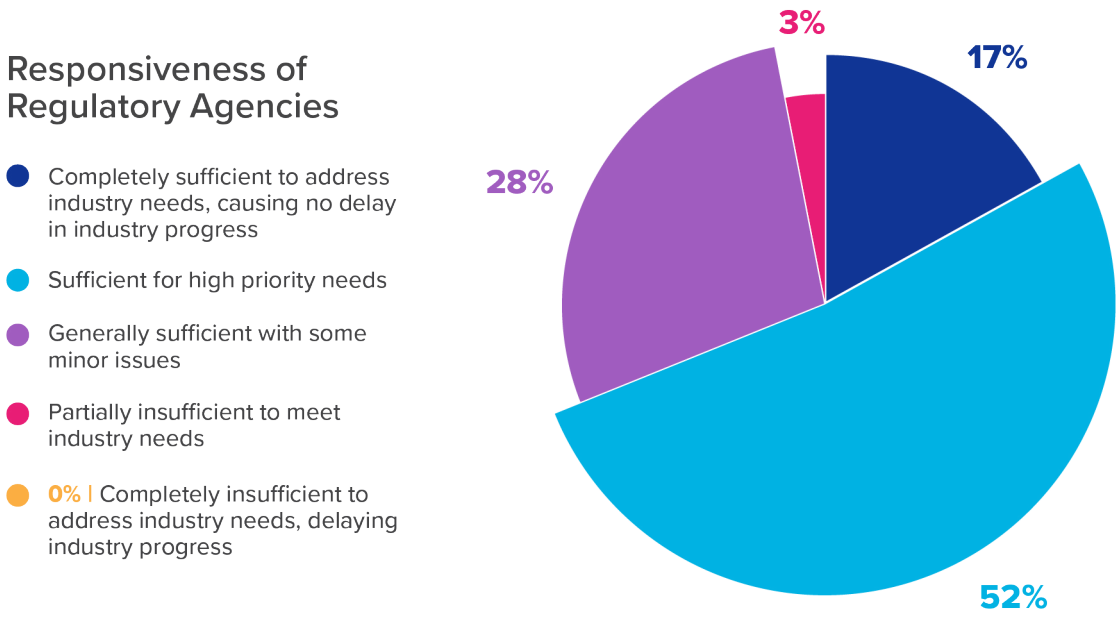
THE REGULATORY ENVIRONMENT IS ACTIVELY EVOLVING TO MEET TODAY'S NEEDS

An advanced therapies "super office" at the Food and Drug Administration (FDA) and an Operation Warp Speed for rare diseases. A long-awaited Annex 1 revision from the European Medicines Agency (EMA), codifying modern best practices for manufacturing sterile products. Recent regulatory approvals based on surrogate endpoints for diseases with no approved therapies, giving drug developers a potential pathway for accelerating discovery and approval.

These ongoing initiatives are evidence of an open-minded and even bullish attitude among regulatory agencies, who appear increasingly motivated to work with drug developers toward solutions for patients with life-threating diseases. Against this backdrop, our survey respondents reported a reasonably positive opinion of regulatory agencies overall (Figure 2.3).

FIGURE 2.3

Globally, how are regulatory agencies responding to the industry's needs?



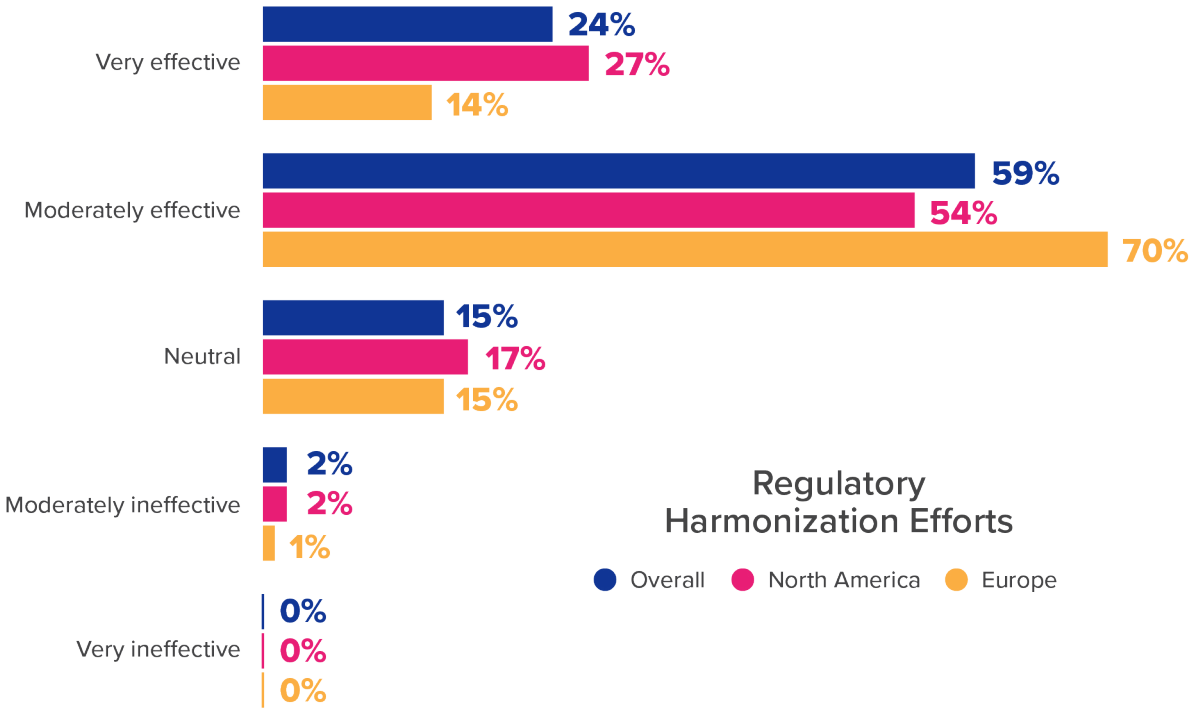
Source: CRB

This cohesion between what the industry needs and what agencies are doing in response could be motivating those early adopters of multimodal facilities noted in Figure 2.2, who seem to be managing the risks of such a pioneering approach in a way that satisfies regulators. This would have been much more difficult in the recent past, before today's modernized regulatory environment prevailed.

A portrait of that modernized environment would not be complete without examining recent harmonization efforts. In general, most survey respondents perceive these efforts somewhere between moderately and very effective (Figure 2.4), though there's an interesting discrepancy between European and North American companies.

FIGURE 2.4

In your opinion, how effective are global regulatory harmonization efforts (PIC/S, Mutual Recognition Agreement, etc.)?



Source: CRB

The more lukewarm response from European companies may reflect the ongoing challenge of harmonization between Member States, both from a regulatory perspective and in terms of the pathway for approving reimbursement in different countries and from different healthcare programs. Regulatory challenges like these are contributing to Europe's declining competitiveness in the cell and gene therapy submarkets—a decline that could be impacting the results of this survey question.

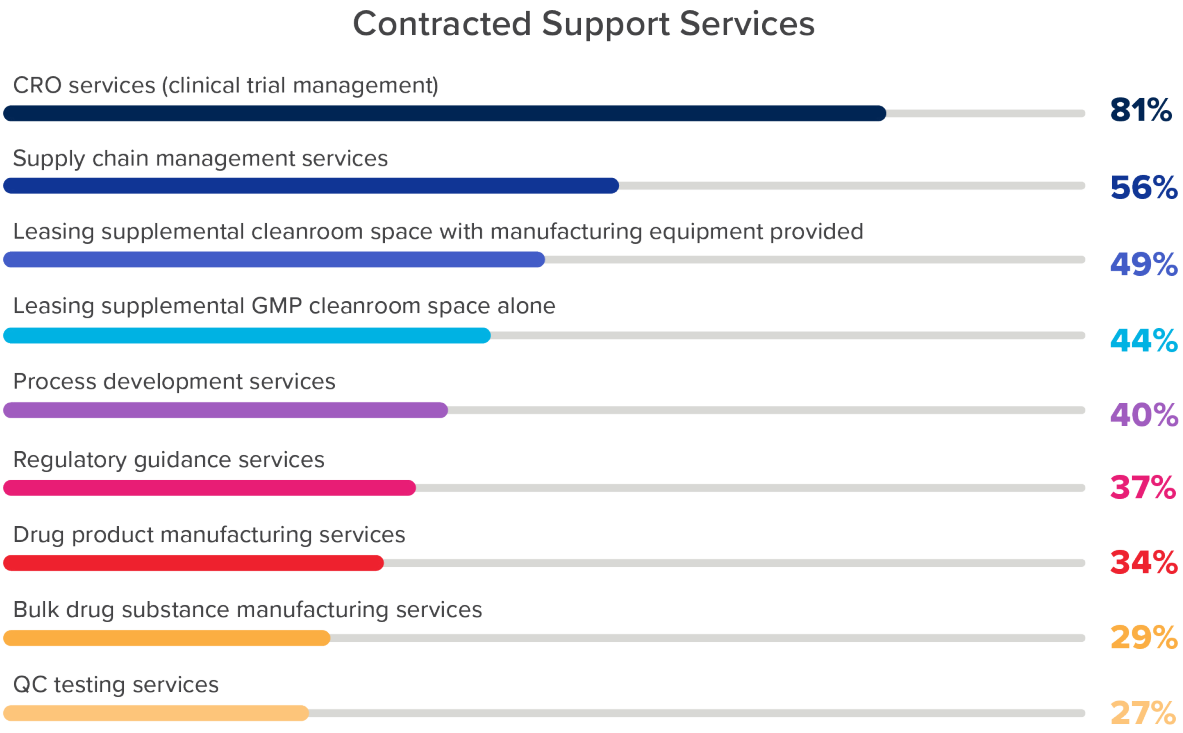
As we'll see in the next section, these challenges appear to be driving European companies to seek out contracted regulatory support services at a higher rate than their North American counterparts.

LONG-TERM CONTRACTOR RELATIONSHIPS ARE AN INCREASINGLY IMPORTANT CONTRIBUTOR TO SUCCESS FOR LIFE SCIENCE COMPANIES

From a broad perspective, life science companies engage with contractors across a variety of upstream and downstream services, with clinical trial management leading demand (Figure 2.5).

FIGURE 2.5

Does your site contract any of the following support services to supplement the operations for your company?



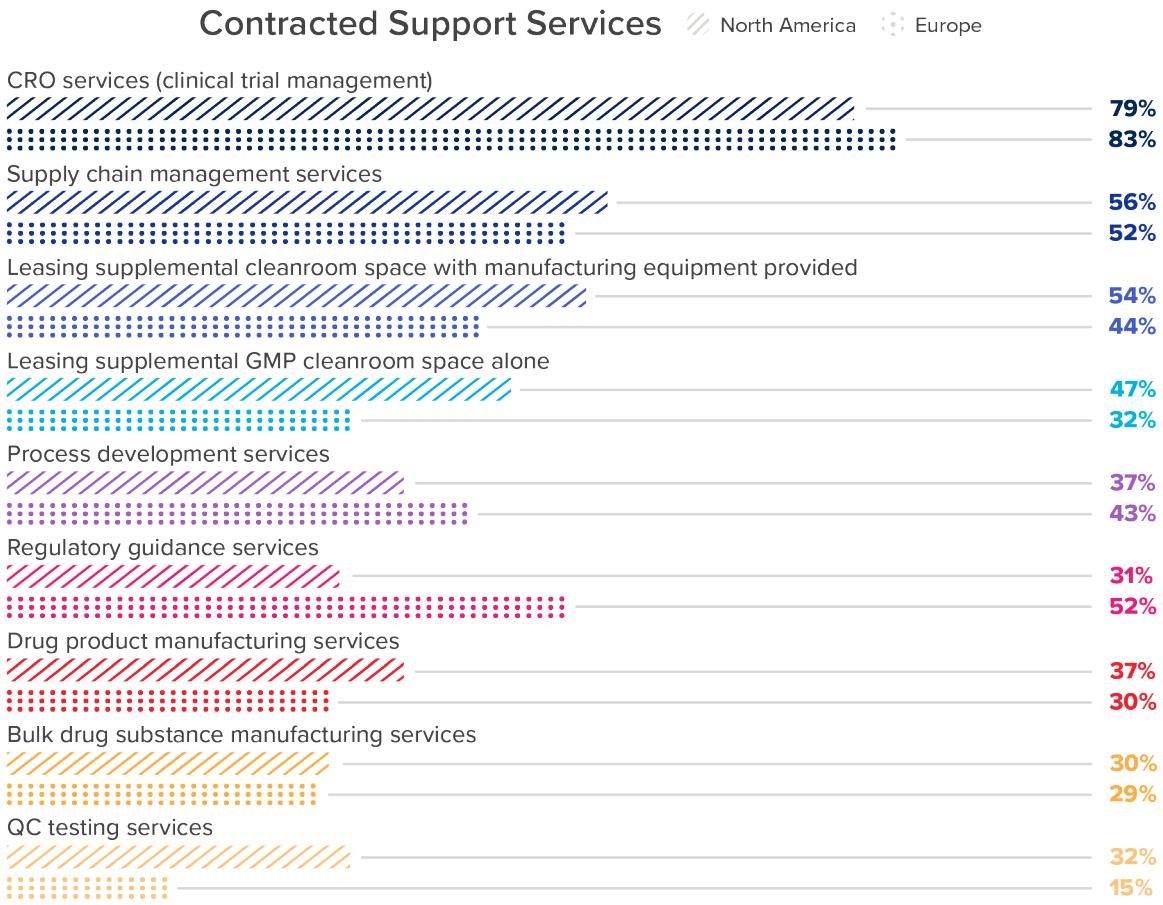
Source: CRB

A closer look reveals insights about the unique challenges facing individual submarkets. When we asked gene therapy developers about their contracting strategy, for example, we noted a much higher demand for CGMP manufacturing services (54%) than the average life science company (34%). Given this submarket's relative infancy, it's no surprise that these companies would choose not to invest in their own capital-intensive manufacturing facilities.

Contracting strategies differ across regions, too (Figure 2.6). As we noted above, life science companies in Europe appear more likely to seek regulatory support from third parties than those in North America.

FIGURE 2.6

Does your site contract any of the following support services to supplement the operations for your company?



Source: CRB

There may be a few reasons for this discrepancy. While the EMA governs the drug approval process with prescriptive rules, the FDA's approach is more interpretive. If companies seeking approval in North America can prove that their approach adheres to the principles of CGMP manufacturing, they may succeed; companies in Europe, on the other hand, must prove their adherence to a strict rulebook, with less leeway for interpretation.

For European companies bringing new modalities to market, this prescriptive regulatory environment can be especially challenging. To get approval, these companies may need to extrapolate their approach based on pre-existing rules, which means navigating significant complexity and engaging in some degree of guesswork. Then there's the issue of tracking and applying local rules unique to certain Member States, making it difficult to operate in multiple countries without a

sophisticated and complex regulatory strategy. In addition to contextualizing their demand for regulatory guidance services, these challenges could explain why our European survey respondents are much less likely than those from North America to expand into new countries over the next five years (9% to 26%).

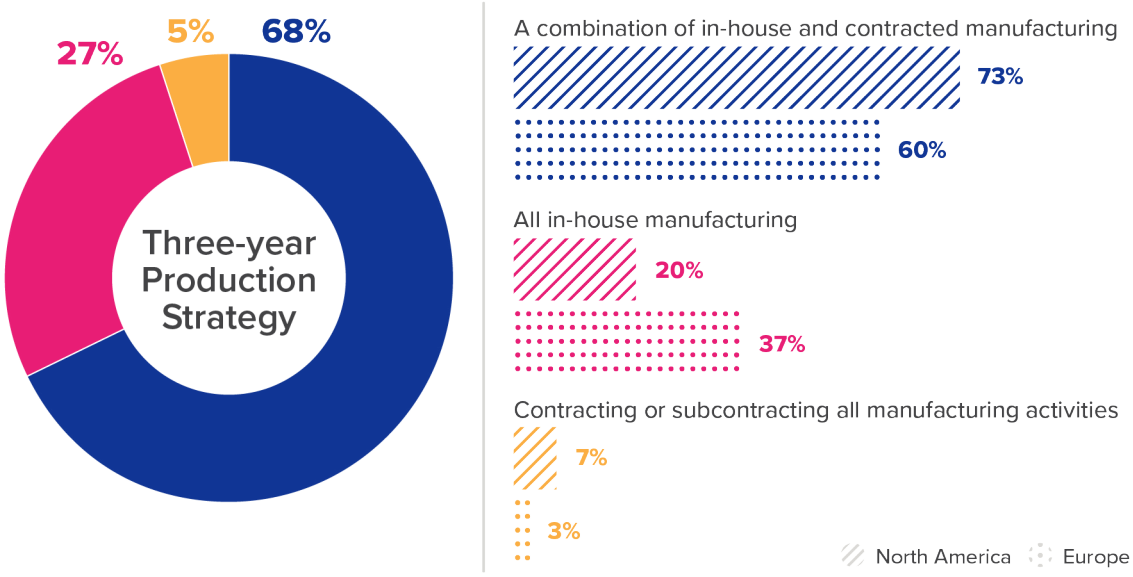
SPOTLIGHT ON CONTRACT MANUFACTURING ORGANIZATIONS (CMOS)

CMOs occupy a particular space within the larger marketplace for contracted services. To understand how today's life science manufacturers are engaging with that space, we asked our survey respondents about their future production strategy.

When we investigated the industry's approach to contract manufacturing in last year's *Horizons: Life Sciences* report, companies appeared to consider CMOs as a core component of their business strategy; nonetheless, the majority still planned to pursue in-house manufacturing only. Though we are cautious about comparing last year's survey group to this year's larger and more diverse respondent pool, our current data reveals a notable evolution: Today, nearly 70% of respondents plan to supplement their in-house capabilities with contracted manufacturing. For startups and small companies in particular, that number jumps to 83%. Even large companies—presumably with more robust in-house capabilities—are more likely than not to engage a CMO (Figure 2.7).

FIGURE 2.7

Which are you most likely to pursue for your site's production strategy in the next three years?



Source: CRB

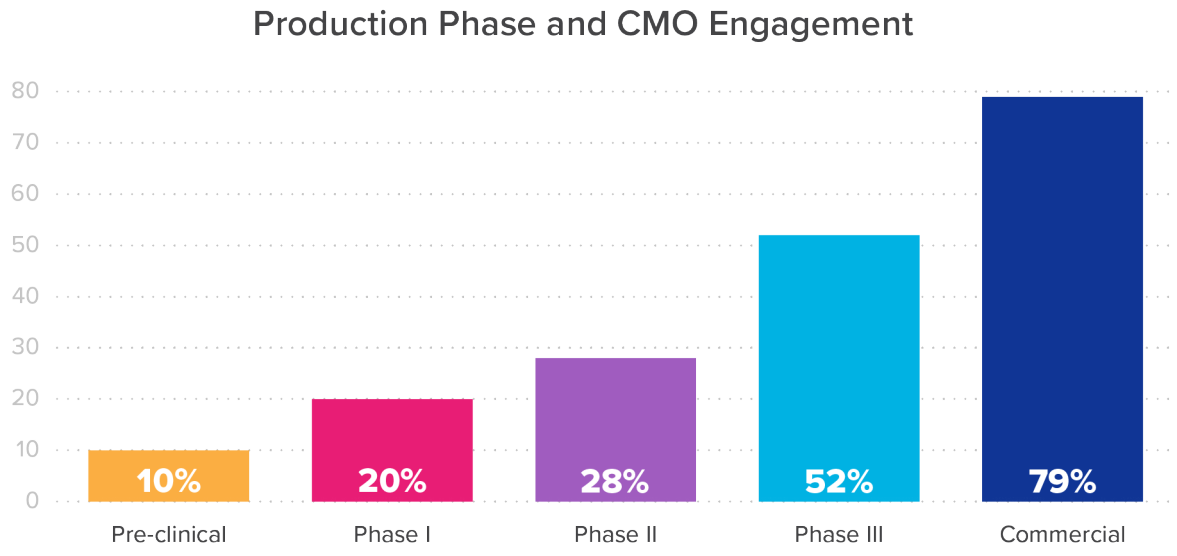
Recent headlines support this observation that demand for CMO services is growing. In June 2023, for example, Pfizer announced a $411 million deal with Samsung Biologics, giving it the necessary manufacturing capacity to support its multiproduct portfolio of biosimilars.

WHEN ARE COMPANIES ENGAGING CMOS?

To better understand the relationship between project owners and CMOs, we asked our respondents to tell us more about the timing around that relationship. From pre-clinical through commercialization, when are they most likely to engage a third-party manufacturer? We learned that the deeper into the manufacturing lifecycle they are, the more likely a life science company is to outsource (Figure 2.8).

FIGURE 2.8

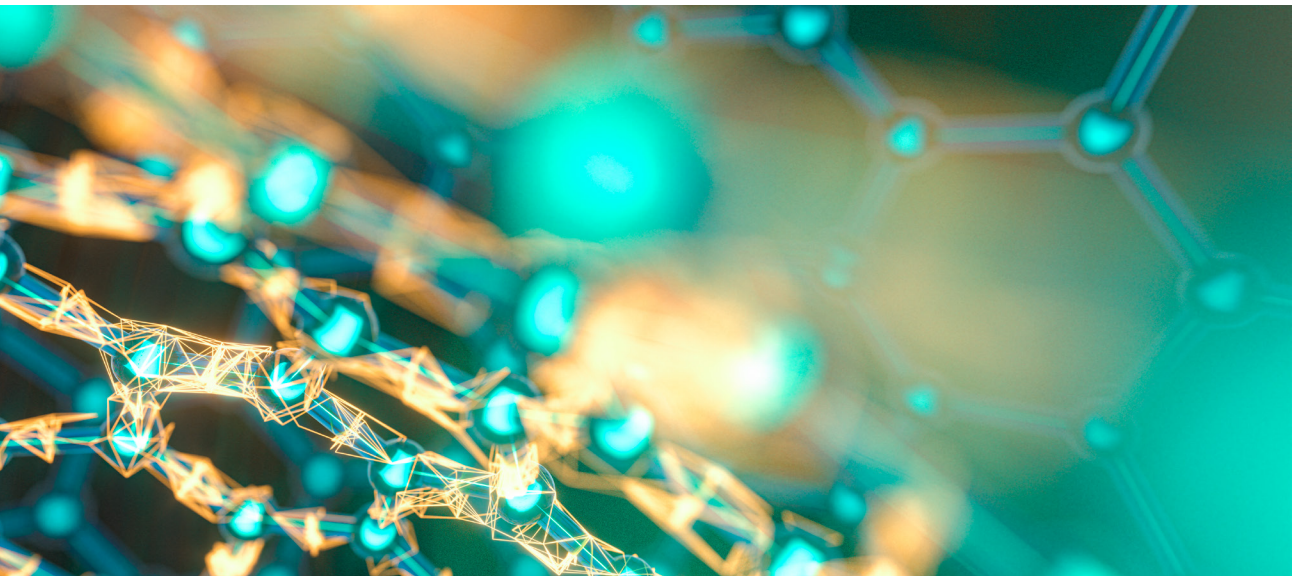
Is your site pursuing/looking to pursue a CMO (or subcontract if you are a CMO) for GMP manufacturing in any of the following phases of production?



Source: CRB

This overall trend likely plays out differently across submarkets. In our experience, for example, startups with emerging therapies in their pipeline and without manufacturing capabilities are likely to partner with a CMO for clinical-scale production, with the goal of bringing manufacturing in-house through a late-phase tech transfer process. In more established submarkets, on the other hand, companies often strive for an ongoing hybrid of in-house capacity and contracted support to manage market fluctuations. That could mean handling core manufacturing components in-house while engaging contractors to supplement that base capacity when necessary, for example.

These varying levels of demand across the life science industry have generated some interesting dynamics in the CMO marketplace. An example we note in the gene therapy article included with this report is that project owners in that submarket perceive an over-saturation of CMO capacity; meanwhile, manufacturers in other submarkets seem to have an insatiable need for extra capacity, incentivizing contract manufacturers like Novartis to expand its global footprint.



Moving cautiously into a promising future

While activity in the life science industry slowed over the last year, our experience with clients suggests that a quiet and focused regrouping has been underway all along. This year's survey results bear that out, revealing an industry that's hard at work in the background of all that economic fluctuation, positioning itself for long-term success.

There's no single way to make that success a reality, but there is a single, compelling reason for companies to continue striving for it: to impact patients and their families, whose well-being depends on access to today's best therapies.

Building on the pandemic response:
Coding RNA for prophylactic and therapeutic vaccines is coming of age

By: Steve Attig and David Estapè

Section 3

The COVID-19 pandemic is infamous for many reasons, but it's remarkable in the way it prompted lightning-fast research, development and production of a global supply of mRNA vaccines. The success of these prophylactic vaccines to protect people could blind us to the fact that mRNA therapeutics are still on the leading edge of biopharmaceutical development. As such, they require more R&D, and a better understanding of how mRNA vaccines are taken up and act in the body; the industry also needs to embrace new technologies and trends to deliver on mRNA's commercial and therapeutic potential.

The responses in this section are from the subset of all those we surveyed who work with coding RNA products and don't include those making non-coding RNA drugs. mRNA drug products can be split into three categories: prophylactic vaccines, therapeutic vaccines and therapeutic drugs. In this year's report the questions we asked focused on the use of mRNA to make prophylactic and therapeutic vaccines.

> *A prophylactic vaccine stimulates immunity in a healthy person to protect against future infectious disease (e.g., the flu or COVID-19).*
>
> *A therapeutic vaccine triggers a patient's immune response to a current disease.*
>
> *A therapeutic drug uses mRNA to direct the synthesis of a functional protein to treat a chronic disease independent of an immune response.*

We canvassed the 39% (n=197) of all respondents who work at a site currently developing and/or manufacturing coding RNA products, a number that respondents anticipate growing to 46% within the next three years. Among those active in coding RNA, 79% are with large- or medium-sized biopharma companies. While there is an equal level of interest in mRNA in North America and Europe, the respondents' views often diverge between these two regions. For this reason, we will often report the results by region.

THE MAJORITY ARE DEVELOPING OR MAKING THERAPEUTIC VACCINES

Almost all (98%) respondents are active in therapeutic vaccines, while 40% are also active in prophylactic vaccines (Figure 3.1). This tells us that while the COVID-19 vaccines opened the door to mRNA vaccines, more effort is now focused on therapeutic vaccines.

Key Takeaways:

- *There are great expectations for future therapeutic vaccine development and production.*
- *72% of Europeans worked at sites focused solely on therapeutic vaccines.*

This result does NOT align with current clinical portfolios of major mRNA companies, in which prophylactic vaccines dominate together with a large number of mRNA therapeutics (which are not included in this survey). It's worth remembering that prophylactic vaccines need to be tested in large numbers of healthy people, making them exceptionally expensive to bring to market. This requires the types of budgets only larger companies have, and startups may choose therapeutic vaccines for this reason. The data reflects this, with more respondents at small (79%) and medium (71%) companies indicating their company is active only in therapeutic vaccines, while large companies cover both types (62%).

There were also regional differences, with those in North America showing greater interest in prophylactic vaccines than their European counterparts (46% vs. 28%), meaning 72% of European respondents said their companies focused solely on therapeutic vaccines. This greater interest in therapeutic vaccines in Europe may be explained by the concerns listed below (Figure 3.3).

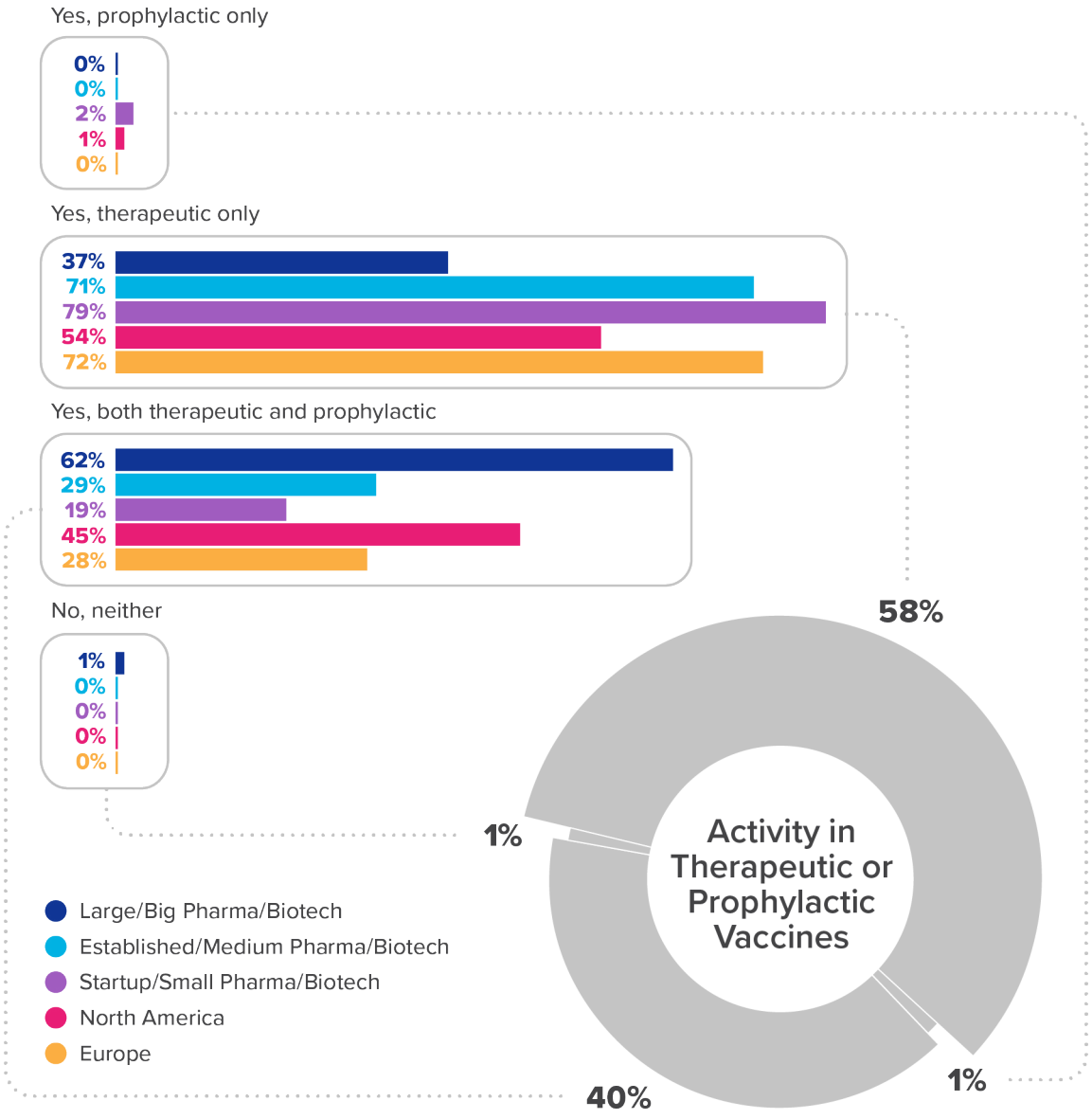
North American respondents show

greater

interest in prophylactic vaccines than their European counterparts

FIGURE 3.1

Is your company active in therapeutic vaccine or prophylactic vaccine modalities?



Source: CRB

WHAT'S IMPORTANT WHEN CHOOSING mRNA FOR VACCINES?

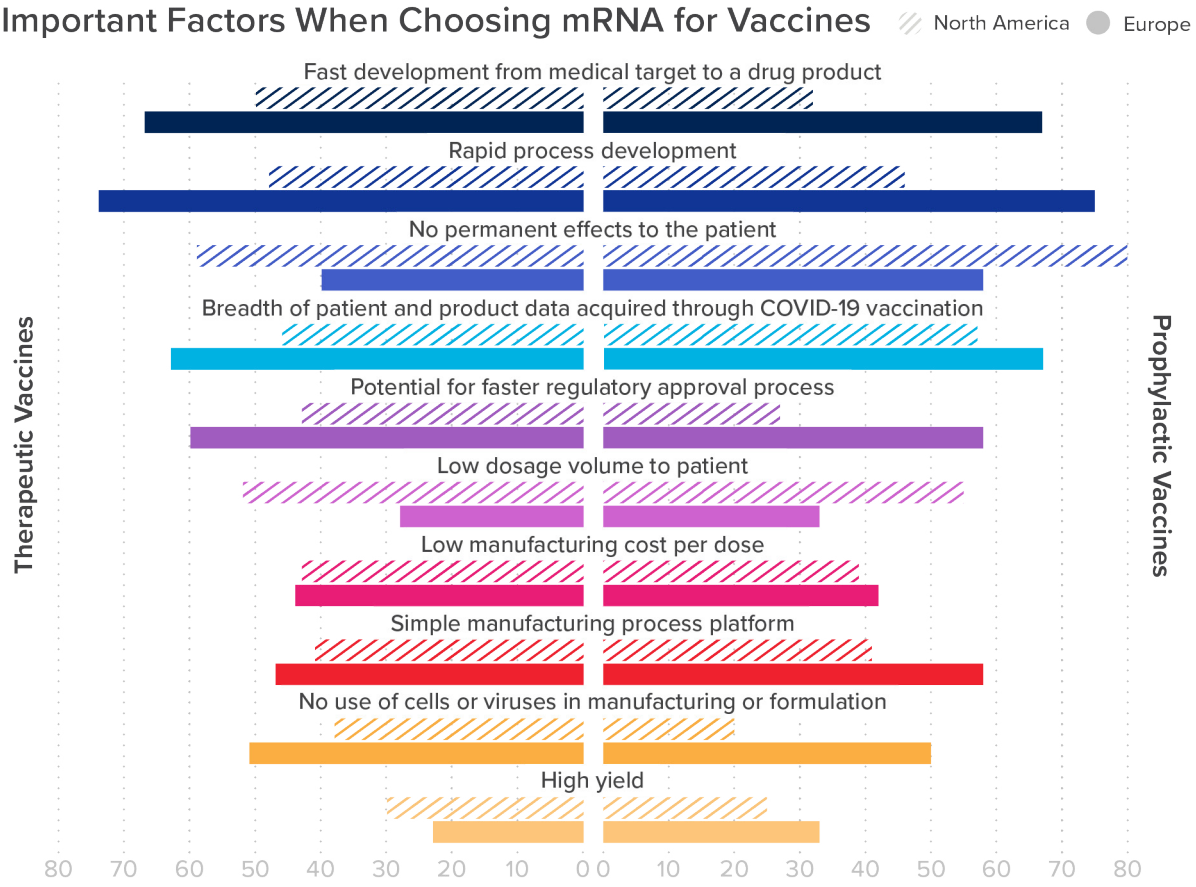
Of the 10 factors we listed as potentially important factors for vaccine modalities, respondents indicated that all of them were relevant (Figure 3.2).

Key Takeaways:

- *Europeans were more likely to rank more factors as "very important" for choosing mRNA for prophylactic vaccines than North Americans.*
- *North Americans value fundamental characteristics of mRNA technology; Europeans focus more on the advantages in the development of mRNA products.*

FIGURE 3.2

How important are the following factors when choosing mRNA over other vaccine modalities?



Source: CRB

There are significant regional differences

When we broke down the results by geography, we saw disparate points of view (Figures 3.2). More than half of those in North America said the following factors were "very important":

1. No permanent effects to the patient (for both prophylactic and therapeutic vaccines)

2. Low dosage volume to patient (for both prophylactic and therapeutic vaccines)
3. Breadth of patient and product data acquired through COVID-19 vaccination (for prophylactic vaccines only)

Generally, European respondents were more likely to choose "very important" in relation to most factors. More than half of respondents from European companies chose faster drug development and process development, the amount of patient and product data from the pandemic and the potential for faster approvals as "very important" factors in their decision to choose mRNA for both therapeutic and prophylactic vaccines. Whereas North Americans value fundamental characteristics of mRNA technology, Europeans focus more on the advantages in the development of mRNA products.

The geographic disparity is even more pronounced for the factors they said were "very important" when choosing mRNA as a modality for making prophylactic vaccines (Figure 3.3). In this case, respondents were more likely to choose the factors listed above, as well as the lack of need for cells or viruses in manufacturing or formulation and the simpler manufacturing process. It's interesting to us that while the Europeans had positive opinions about most factors related to prophylactic vaccines, only 28% of them said their company was active in this modality (Figure 3.1). This suggests decisions about pursued modality may be related more to economic and business factors rather than R&D advantages.

Most said low manufacturing cost per dose didn't matter. Does it?

Only 45% picked low manufacturing cost per dose as a "very important" factor when choosing mRNA over other modalities for therapeutic vaccines and only 37% for prophylactic vaccines. This suggests that lower manufacturing cost was not seen as a major competitive advantage. We wonder, however, if it *could* become an advantage if those costs were lowered significantly. In fact, manufacturers of large volumes of prophylactic vaccines are indicating that cost is possibly the most important consideration for them.

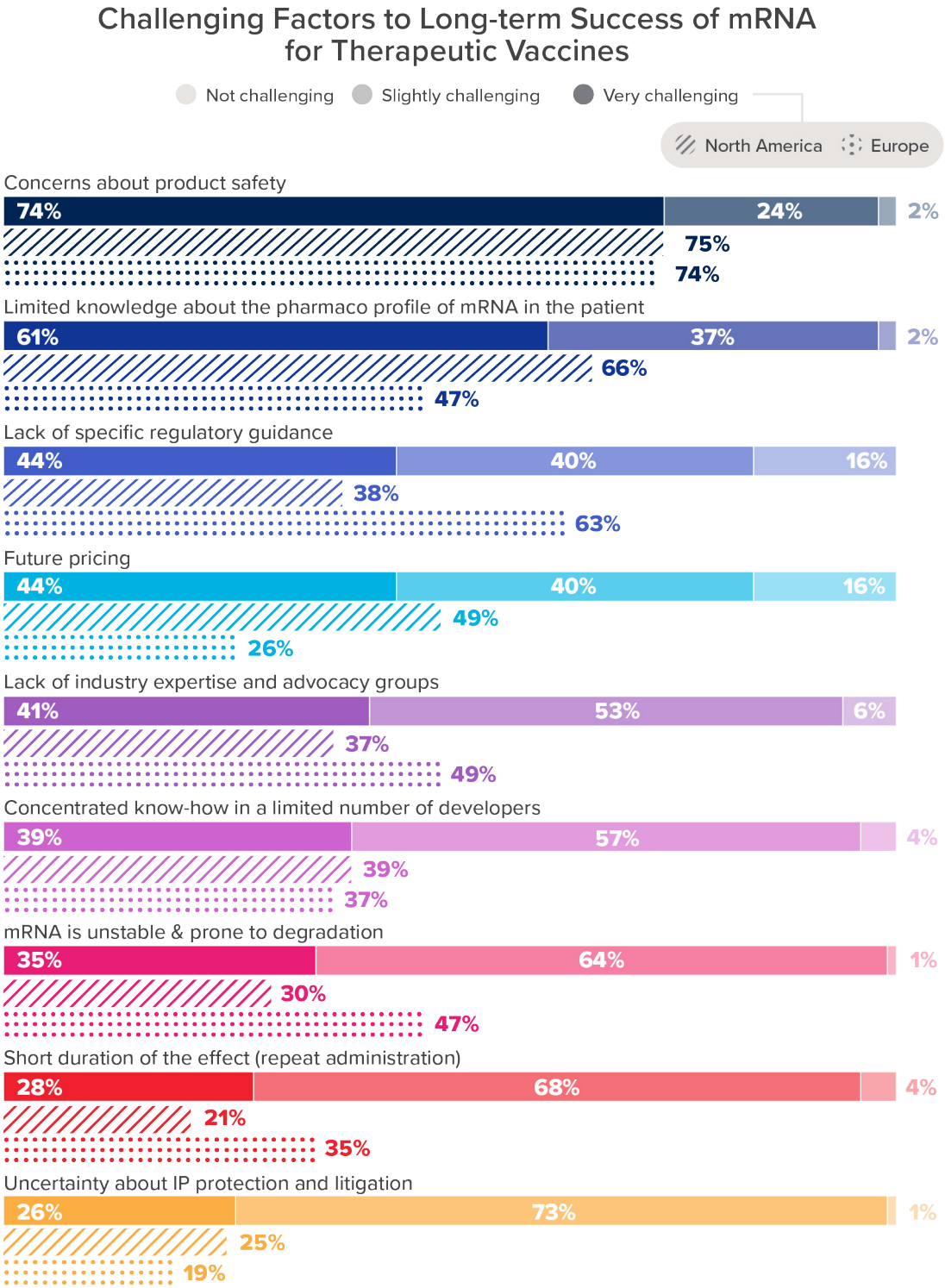
Although it was low dosage volume per patient and high yields that drove the supply of COVID-19 vaccines in record time, significantly less than half of respondents consider these to be "very important" factors when considering mRNA or other modalities.

THE TOP CONCERNS ARE PRODUCT SAFETY AND LIMITED KNOWLEDGE OF HOW mRNA VACCINES BEHAVE IN PATIENTS

Roughly three-quarters of respondents felt product safety is "very challenging" for both types of vaccines (Figure 3.3). Another top concern was the limited knowledge about the pharmacokinetics/pharmacodynamics (PK/PD) of mRNA in patients, which 54% and 61% indicated as "very challenging." These two concerns likely reflect the novelty of these modalities and the questions that continue to exist to better understand how mRNA products are taken up and act in the body.

FIGURE 3.3

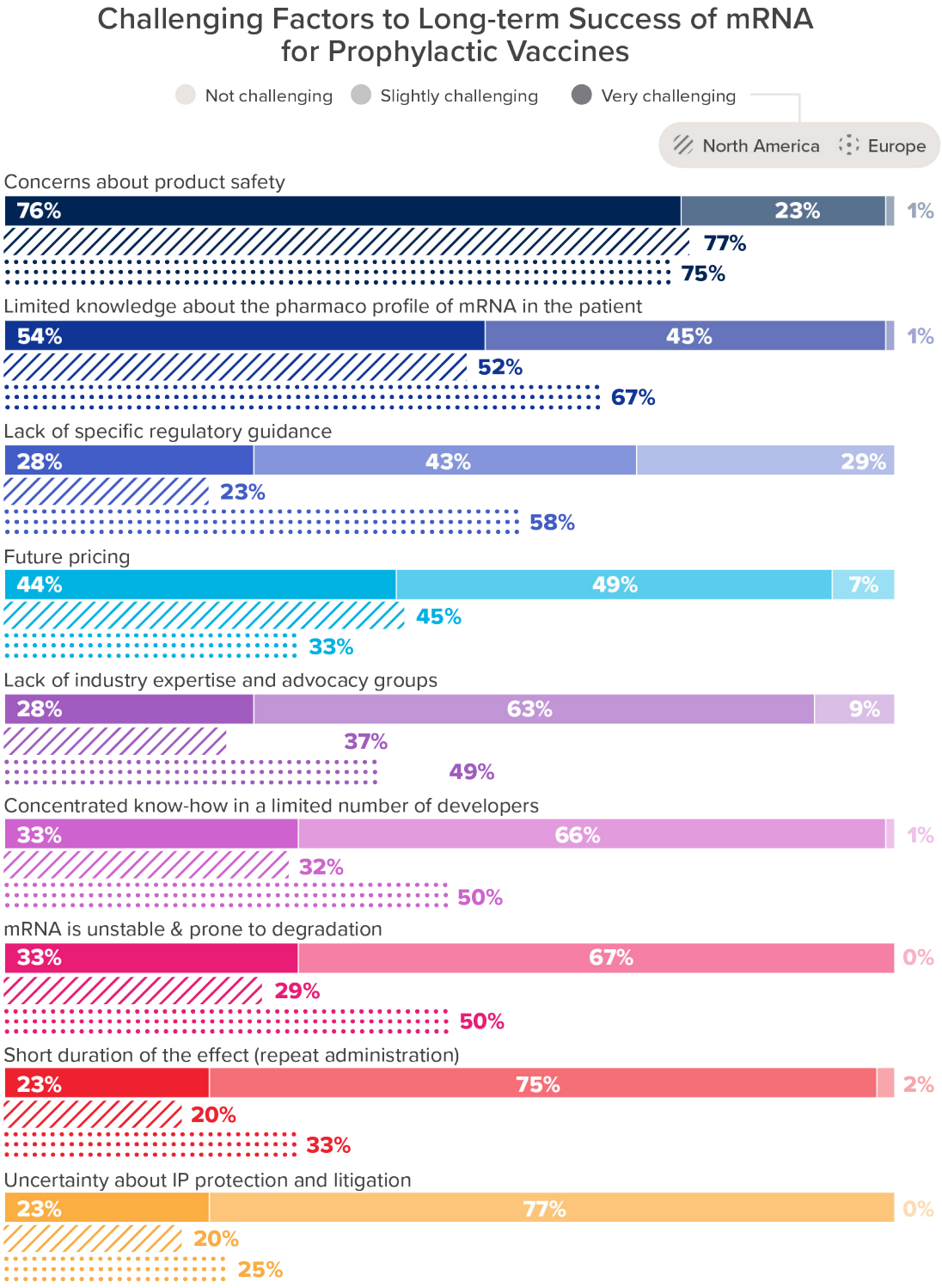
How challenging are the following factors to long-term success of mRNA vaccines?



Source: CRB

FIGURE 3.3 CONTINUED

How challenging are the following factors to long-term success of mRNA vaccines?



Source: CRB

Key Takeaways:

- *The top concerns are product safety and limited knowledge of how mRNA vaccines behave in patients.*
- *Europeans find the challenges greater, especially for prophylactic vaccines.*

In general, a larger percentage of European respondents chose "very challenging" for most factors, particularly for prophylactic vaccines, in keeping with lower interest among this group for this type of vaccine. Europeans also had much greater concern about most challenges for both vaccine types than respondents in North America, particularly for lack of regulatory guidance and the instability of mRNA (Figure 3.3). The only challenges for which there was greater concern in North America were future pricing of both types of vaccine and limited knowledge of the PK/PD profile of therapeutic vaccines. Future pricing concerns may be exacerbated by the price increases of the COVID-19 vaccines seen after the pandemic.

IP protection and lack of skilled workers are not major challenges

There were a few factors seen as less challenging. Only about one-quarter of respondents indicated that the uncertainty of IP protection and litigation were challenges to the long-term success of mRNA vaccines. This is surprising to us given the ongoing litigation about the IP of the COVID-19 vaccines and may reflect the large number of respondents in R&D. The concentrated know-how in a limited number of developers—and the competition for skilled workers that this implies—were considered less of a challenge than many other factors. Finally, the short duration of the effect and the need for repeat administration were also seen as less of a challenge than other factors.

PROCESS CHARACTERIZATION AND QUALITY CONTROL ARE THE MAIN AREAS WHERE PROGRESS IS NEEDED

We asked industry experts what is needed to support the development of mRNA vaccines. The two that topped the list for all respondents were RNA-specific analytical tools and RNA-specific critical quality attributes (CQAs) and critical process parameters (CPPs) (Figure 3.4). These choices were much more pronounced among those in North America (61% and 50%) than those in Europe (26% and 14%).

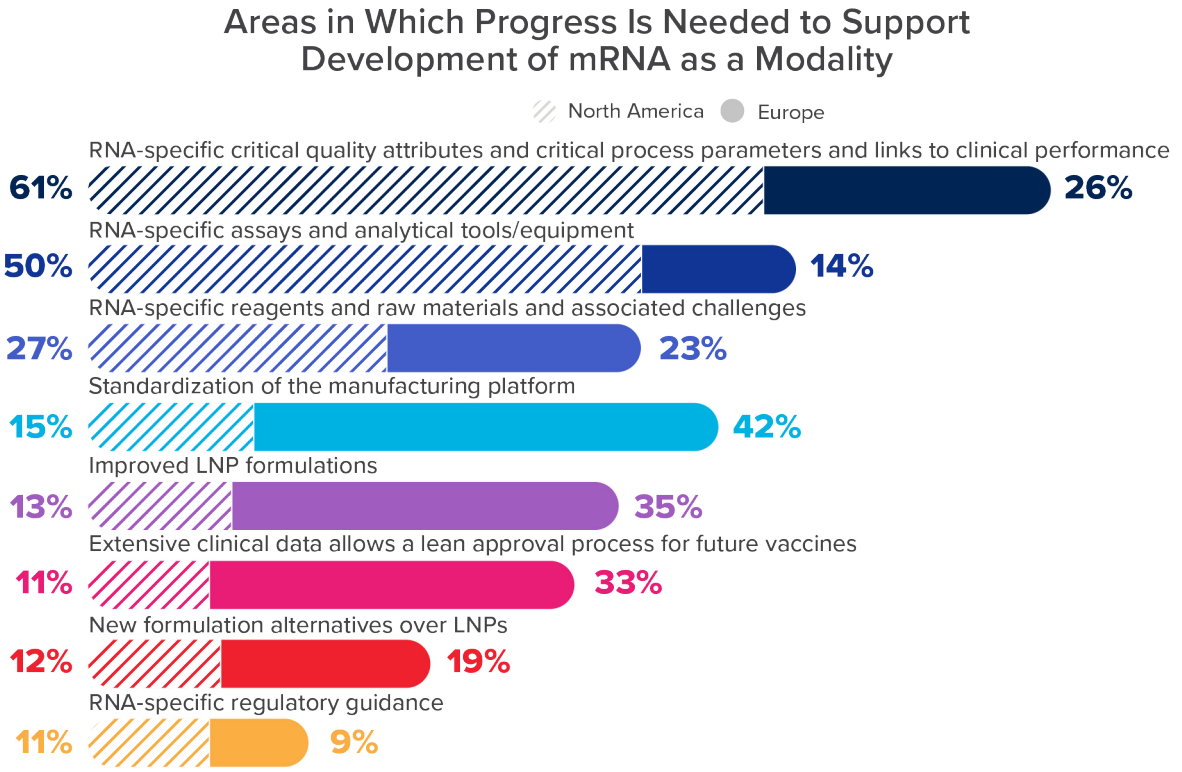
These responses align with the concern about product understanding and safety discussed previously. They're also aligned with the preparation of pharmacopeia monographs for mRNA in both Europe and North America, which shows progress in these key areas and provides clarity for future R&D of mRNA-based products.

The regional data also show those in Europe were more likely to indicate progress is needed to standardize the manufacturing platform, improve LNP formulations, and the need for extensive clinical data to streamline the approval process for future vaccines.

Together, this data suggests a need for more R&D, particularly in process development. Those in North America, at least, consider the industry to still be near the beginning of this journey, requiring much more research. In Europe, the respondents were looking to a future with standardized manufacturing, better mRNA delivery systems and enough experience with mRNA vaccines to speed up the approval process.

FIGURE 3.4

To support the development of mRNA as a modality, what are the two biggest areas in which progress is needed?



Source: CRB

NEW TECHNOLOGIES ARE ON THE NEAR HORIZON

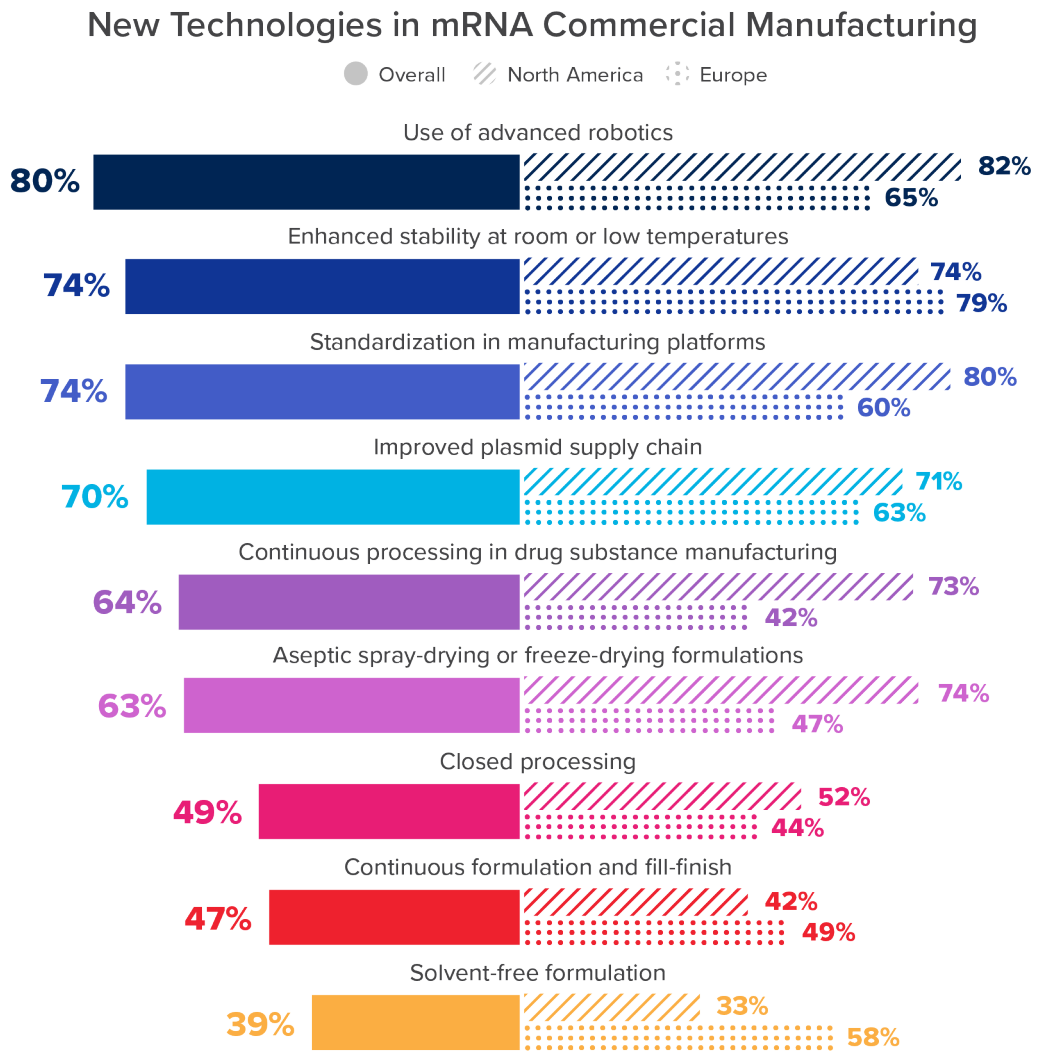
Respondents indicated that all nine of the new technologies listed were relevant (Figure 3.5), with robotics, enhanced mRNA stability, standardization of manufacturing platforms and an improved plasmid supply chain topping the list.

Between regions there was consensus on the likelihood of seeing enhanced stability, an improved plasmid supply chain, closed processing and continuous formulation and fill-finish within five years (Figure 3.5). North American respondents were

more optimistic about the likelihood of robotics, continuous processing in drug substance manufacturing, standardized manufacturing platforms, and aseptic spray-drying or freeze-drying formulation, while those in Europe were more optimistic about the implementation of solvent-free formulation.

FIGURE 3.5

Do you expect to see the implementation of the following new technologies in the next five years for the manufacturing of mRNA drug substance or product?



Source: CRB

Key Takeaway:

- *Both regions share similar expectations about new technologies and future trends in the short and long term.*

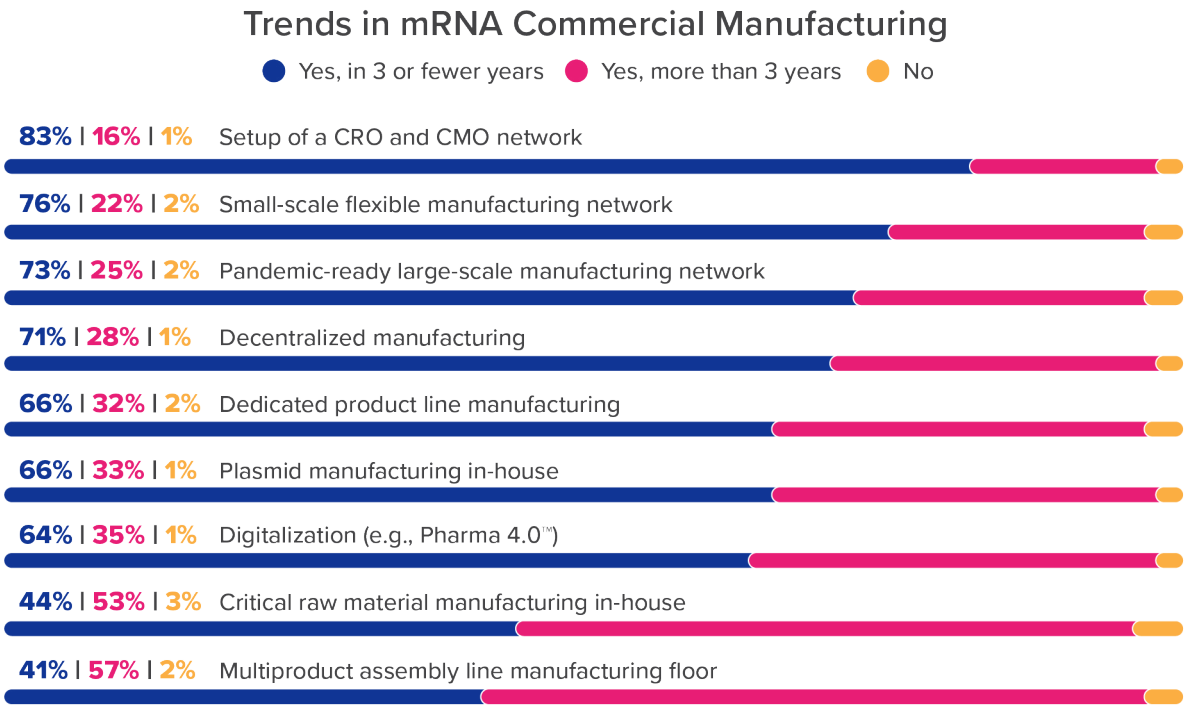
WHAT TO WATCH FOR IN mRNA COMMERCIAL MANUFACTURING

We asked respondents which of nine potential trends in mRNA commercial manufacturing they foresee being implemented (Figure 3.6). The good news is that virtually everyone sees these developments being realized, with the majority expecting to see most of these trends arrive in the next three years. There is convergence between North America and Europe for all of these three-year trends except decentralized manufacturing and digitalization (Figure 3.6). While almost two-thirds of all respondents selected digitalization to be in place within three years, only 44% of Europeans believed this to be true. And the numbers for decentralized manufacturing are even more striking, with 79% of North Americans and only 44% of Europeans expecting this within three years.

Decentralized manufacturing and digitalization are related and act synergistically. We know large prophylactic vaccine manufacturers are currently working on extending their manufacturing platforms and building partnerships worldwide, and we expect this to occur in both Europe and North America. BioNTech is developing BioNTainers to allow scalable mRNA vaccine production anywhere in the world, including its first in Africa. Decentralized could be understood as multiple facilities within one or many geographical locations, as well as engaging CRO and CMO partners, which was the top-picked three-year trend of all (83%).

FIGURE 3.6

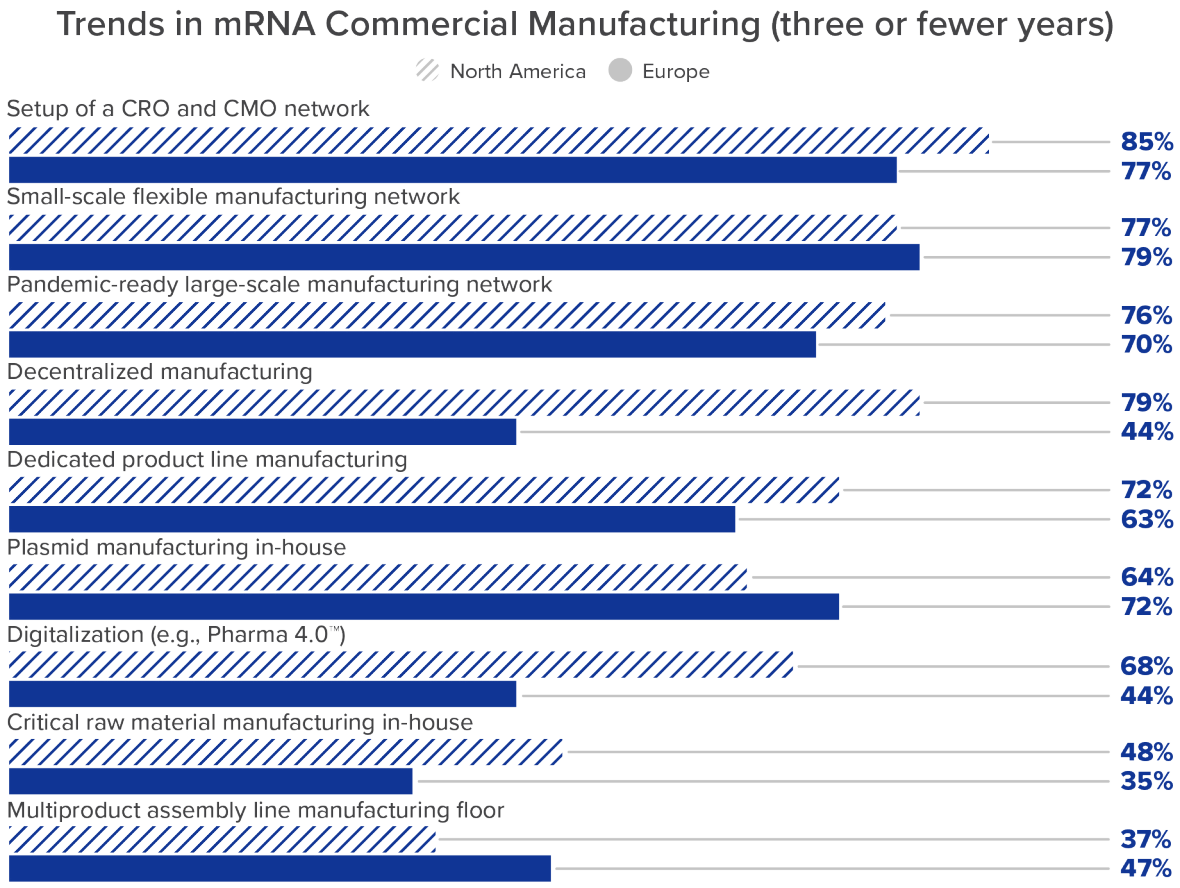
Do you expect to see the following trends in mRNA commercial manufacturing within the next several years?



Source: CRB

FIGURE 3.6 [CONTINUED]

Do you expect to see the following trends in mRNA commercial manufacturing within the next several years?



Source: CRB

The enthusiasm for mRNA continues

In last year's *Horizons: Life Sciences Report* we noted a positive outlook among those in the industry for RNA-based therapies. This year, we shifted our focus onto coding RNA for therapeutic and prophylactic vaccines—and we see a similar enthusiasm. The responses suggest that a wave of therapeutic vaccine development and manufacturing will wash over the industry in the next five years, while the expansion of prophylactic vaccines continues alongside. Even with pronounced differences in their opinions on the pros and cons of mRNA technology, both the Europeans and North Americans are aligned on the key trends and technologies we'll soon see to meet any challenges.

Medicine at the speed of cells:

What will it take for cell therapy manufacturers to commercialize faster and reduce turnaround times?

By: Michela Castellani-Kleinschroth and Peter Walters

Section 4

In the early days of cell therapy research and development, these novel products were the domain of small- and medium-sized pioneers. Today, the landscape has changed. Many “big pharma” companies include cell therapies in their product pipeline. In fact, in our survey of 500+ companies from across the life science industry, more than three in four respondents (83%) have products in this area. What was once a boutique technology has grown into a promising opportunity for companies of all sizes.

This momentum has paid off. An allogeneic cell therapy from Atara Biotherapeutics recently became the first in the world to receive approval from the European Commission, for example. Cartesian Therapeutics has reached Phase II clinical trials with a first-in-class cell-based CAR-T therapy targeting neurological diseases. Breakthroughs like these are emerging regularly.

Clearly, this submarket has the potential to generate meaningful patient outcomes. To realize that potential, cell therapy manufacturers need to answer three key questions:

1. How can we accelerate commercialization?
2. How can we reduce the turnaround time between the bedside and the bench?
3. How will evolutions in gene editing technologies help to get cell-based therapies to market faster?

North American and European manufacturers may approach these questions differently, but they share a single objective: to standardize CGMP manufacturing via the most advanced and efficient technologies available, which in turn will mean simpler manufacturing processes, faster results and more hope for patients facing grave illness.

1. ACCELERATING COMMERCIALIZATION

For patients, cell therapies are a potential lifeline. For example, the cell-based cancer therapy Kymriah® generated buzz in 2012 when a six-year-old became the world's first pediatric patient to receive it (she's still cancer-free), sending a message of hope around the world. Meanwhile, patients facing diabetes can take courage from the FDA's recent approval of an allogeneic islet cell therapy. These and other promising therapies are the driving force behind this industry.

To continue supporting patients in these life-changing ways, cell therapy manufacturers need to close the gap between the lab and the commercial-scale manufacturing environment—a gap rife with risks and potential delays, particularly for those who are not fully prepared for that transition.

What does it mean to be "fully prepared"? Often, it comes down to a proactive strategy that addresses two key areas:

- Early engagement with the appropriate regulatory agencies
- Early adoption of a CGMP state of mind

Today's cell therapy manufacturers have adopted these strategies. In fact, their survey responses reveal a proactive approach to the challenges of commercialization and a willingness to address those challenges even earlier in the project delivery process.

Regulatory consultation as a gateway to compliance

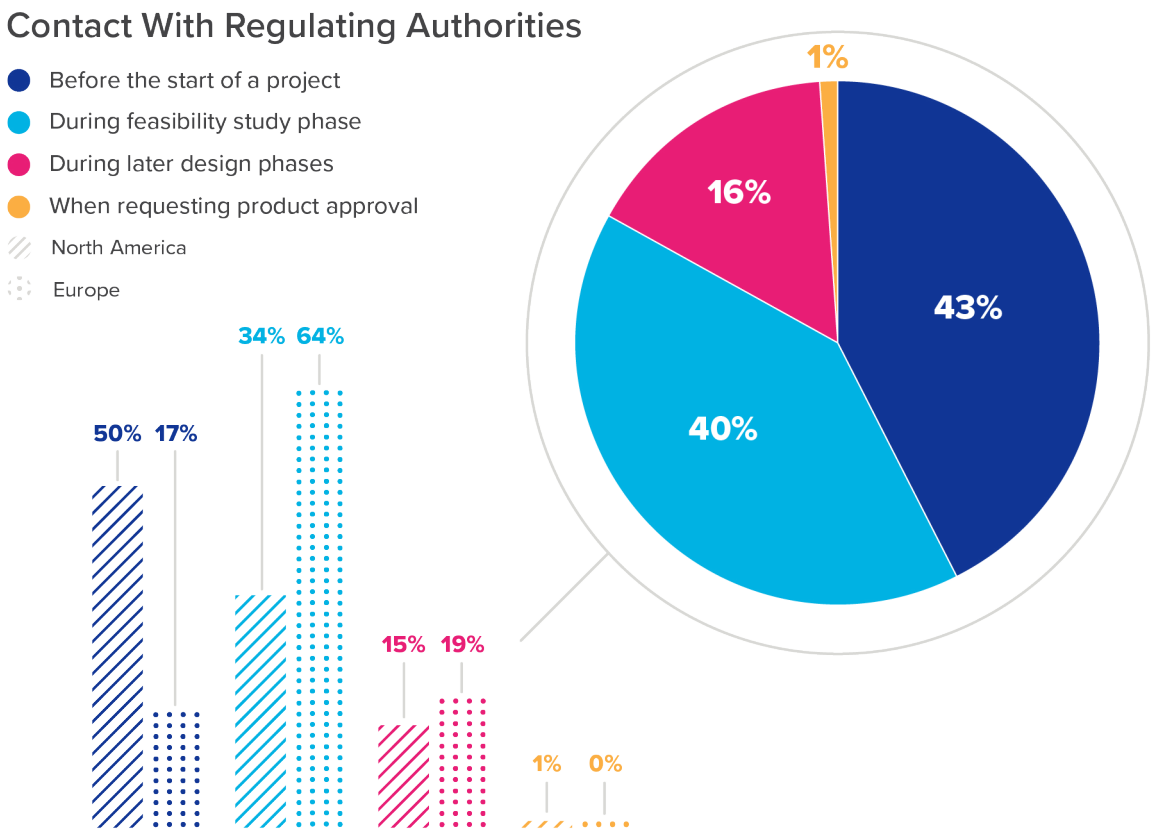
A successful regulatory experience often comes down to timing. Early engagement with regulators gives manufacturers room to discuss new directions, solicit expert guidance and understand exactly how to meet requirements before committing real-world resources to a project.

In terms of overall numbers, our survey uncovered a groundswell of support for this "early engagement" strategy. Nearly half of respondents typically contact the relevant regulatory authorities before starting a new project (Figure 4.1).

Look closer, though, and some interesting dynamics emerge. Manufacturers in the North American market are much keener to engage regulators early than those in Europe, where later engagement—as late as the design phase for a fifth of European respondents—is more typical.

FIGURE 4.1

When does your company typically contact relevant regulating authorities for planned facilities or therapies?



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It's not that manufacturers in North America and Europe have vastly different attitudes toward the regulatory environment. In fact, when we asked how well regulatory agencies are responding to the needs of the cell therapy sub-market, manufacturers in both markets responded positively.

Instead, this regional difference may have to do with nuances in the European regulatory market. These nuances include:

- **A developing pathway for "unofficial discussions" in Europe**

  Regulatory authorities in Europe are working to encourage early engagement through programs like the EMA's Innovation Task Force (ITF), which is similar to the FDA's INTERACT pre-IND meeting. A new Joint Clinical Assessment (JCA) is also set to emerge at the Europe level, giving manufacturers of advanced therapy medicinal products (ATMPs) a pathway for reducing duplicative reviews in Member States.

These initiatives are part of a shift toward a proactive and progressive environment in which project owners and regulators communicate early, although it seems that companies in Europe have not embraced that concept as fully as their North American counterparts.

- **Recent changes in the European regulatory landscape**

  Regulating agencies in Europe recently acknowledged the need for updated legislation that promotes accelerated access to cell therapies. The EMA's Annex 1 revision is an example, giving manufacturers of sterile products a framework for addressing contamination control and meeting CGMP requirements.

  As these changes unfold, European cell therapy developers may feel pressure to comply with both today's requirements and those that may emerge tomorrow, which could incentivize extensive due diligence before engaging regulators.

- **Local variations in regulatory requirements across Europe**

  The Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S) is working to deepen global harmonization efforts, but more work is needed at the local regulatory level to ensure that unreasonable roadblocks are not impacting patient populations with little other hope.

  This scenario is notable in Europe, where the complexity of local regulations can make it difficult for cell therapy developers to commercialize in different European countries. It's possible that this complexity is another reason why manufacturers in Europe are more inclined to establish a detailed project analysis before approaching regulators.

Each of these possible explanations adds up to one overarching theme: the regulatory environment in Europe is complex and rapidly changing. Many of those changes aspire to improve the regulatory pathway.

As these developments take shape, the fact remains that early consultation with regulators can afford manufacturers a smoother path to compliance. Several regulatory initiatives are underway to encourage this approach, though more is needed to make early engagement part of every company's approval strategy.

Key Takeaway:

A proactive and consultative regulatory strategy is key to removing barriers from your pathway to commercialization—and fewer barriers means fewer delays, surprise costs and negative patient impacts.

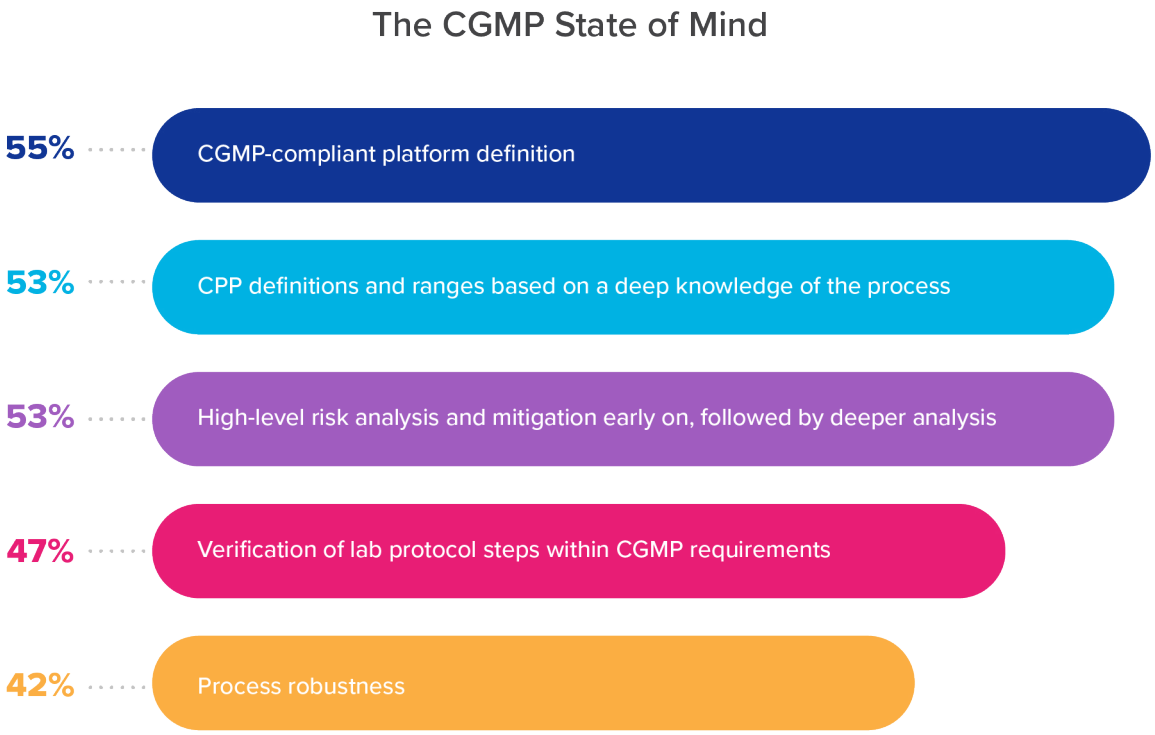
Bridge the lab-to-commercialization gap with a "CGMP state of mind"

Taking the time during process development to scrutinize every decision through the lens of CGMP manufacturing helps to ensure a successful transition to commercial-scale production from day one.

How, exactly, can manufacturers apply a CGMP lens while still operating in an R&D space? For our survey respondents, there's no single answer. Instead, manufacturers appear to be giving relatively equal attention to several mission-critical CGMP considerations, with the overall goal of implementing a robust strategy from the early stages of program development (Figure 4.2).

FIGURE 4.2

Does your company use any components of adopting a "CGMP state of mind" (i.e., Current Good Manufacturing Practice to make the process compliant, scalable, safe and fast) when planning for, or entering, a Clinical Phase II progression?



Source: CRB

By threading each of these components into their plan, manufacturers can position their cell therapy project for a faster transition to the commercial-scale environment. The most important of these components include:

- **CGMP-compliant platform (55%)**

  Manufacturers who develop CGMP-ready lab protocols and use them as the foundation for a simple, standardized platform can later leverage key advantages, like extensive automation and process closure.

  They are also well-positioned for pipeline flexibility, since a robust platform can typically support other products within the same modality. Such a platform can also make contracted manufacturing more feasible—a strategy that 68% of our survey respondents include in their three-year site plan.

- **CPP definitions and ranges (53%)**

  Critical process parameters (CPPs) are especially important for manufacturers of autologous cell therapies, which depend on source material that is harvested from patients and therefore susceptible to variability.

- **High-level risk analysis (53%)**

  With a standardized platform in place early and a clear definition of CPPs, manufacturers can undertake a detailed risk analysis early in the process development phase. This will proactively eliminate roadblocks from the pathway to commercialization and ensure ongoing process robustness.

Key Takeaway:

Use the principles of CGMP manufacturing to assess, modify and optimize processes while still in the lab, which will improve readiness for the regulated environment.

2. REDUCING TURNAROUND TIME

As the promise of curative cell therapies propels the industry forward, a headwind of logistical challenges is slowing it down. This is especially true for autologous cell therapies, which rely on a complex bench-to-bedside process. The greater the distance between patient and facility, the longer this process becomes, with consequences for manufacturers, point-of-care teams and patients.

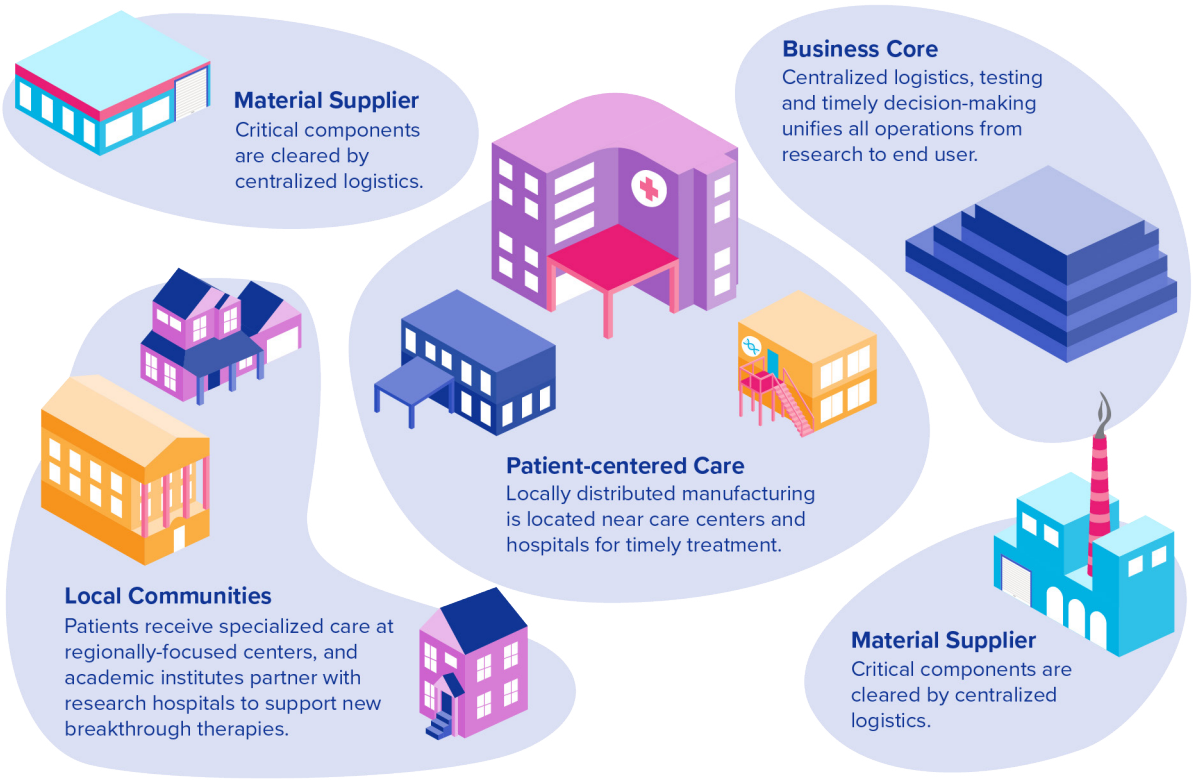
A new manufacturing strategy is emerging that could ease some of these challenges: decentralized cell therapy manufacturing.

Decentralized manufacturing shrinks the distance between manufacturers and patients

If cell therapy manufacturers could transplant their CGMP capabilities to a cleanroom at or near the point of care, they could dramatically shrink the time required to

produce life-saving therapies. That's the idea behind decentralized cell therapy manufacturing.

There are many possible variations, but the basic model looks like this:



A central CGMP facility

- Responsible for remotely releasing all drug product batches manufactured at local sites, and for identifying and handling deviations
- Establishes all standard operating procedures (SOPs) and the quality management system (QMS), which are duplicated at local sites

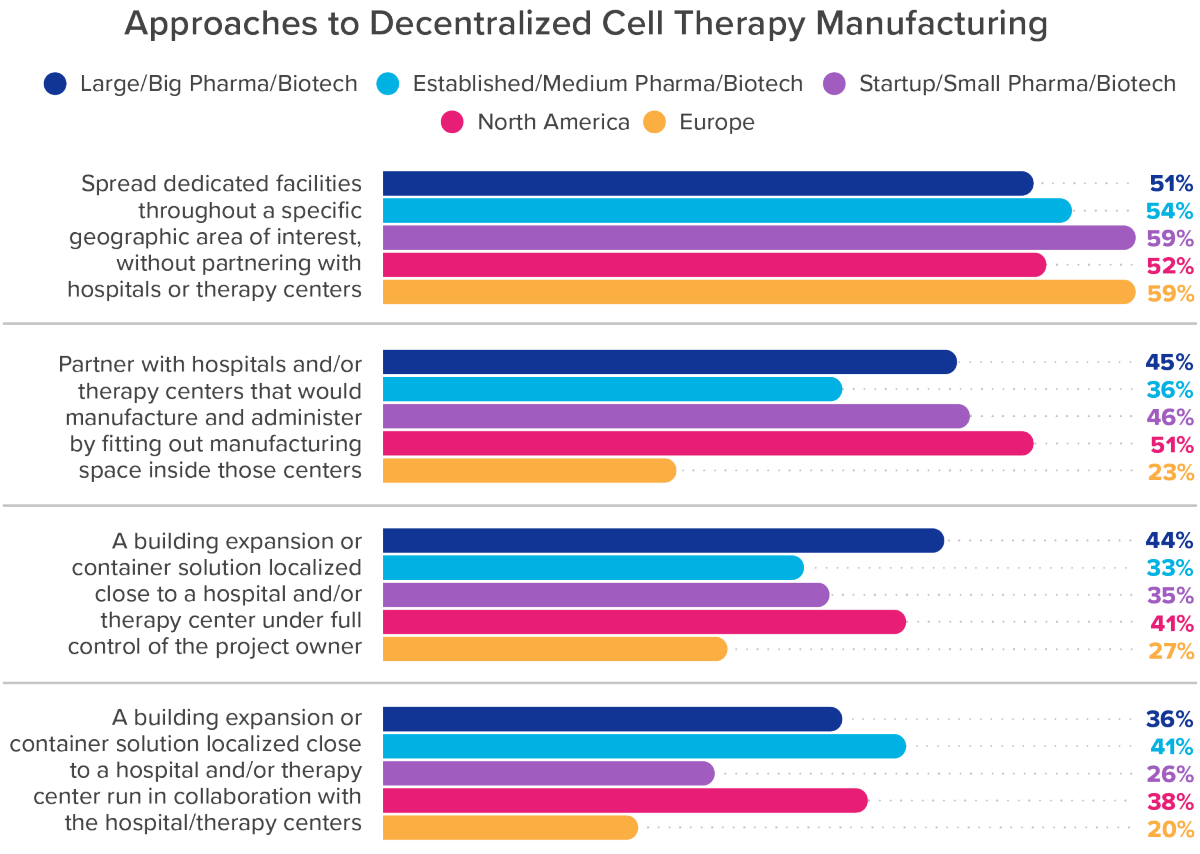
Small, local clones of the central facility

- Responsible for CGMP compliance and batch documentation
- Located close to the point of care
- Follow the central site's SOPs and QMS

To get a sense of how close we are to mainstream decentralization, we asked our survey respondents about their own approaches. The result reveals an overall interest in the concept, with some notable nuances between regions (Figure 4.3).

FIGURE 4.3

Would your company consider using any of the following potential approaches to decentralized manufacturing for cell therapy?



Source: CRB

In North America, manufacturers appear interested in each potential approach to decentralization, including the most integrative model that involves locating CGMP spaces directly inside a hospital. European manufacturers show a strong inclination for decentralized "lite"—that is, the idea of increasing the number of dedicated facilities and locating them near (but not at or in) hospitals or therapy centers.

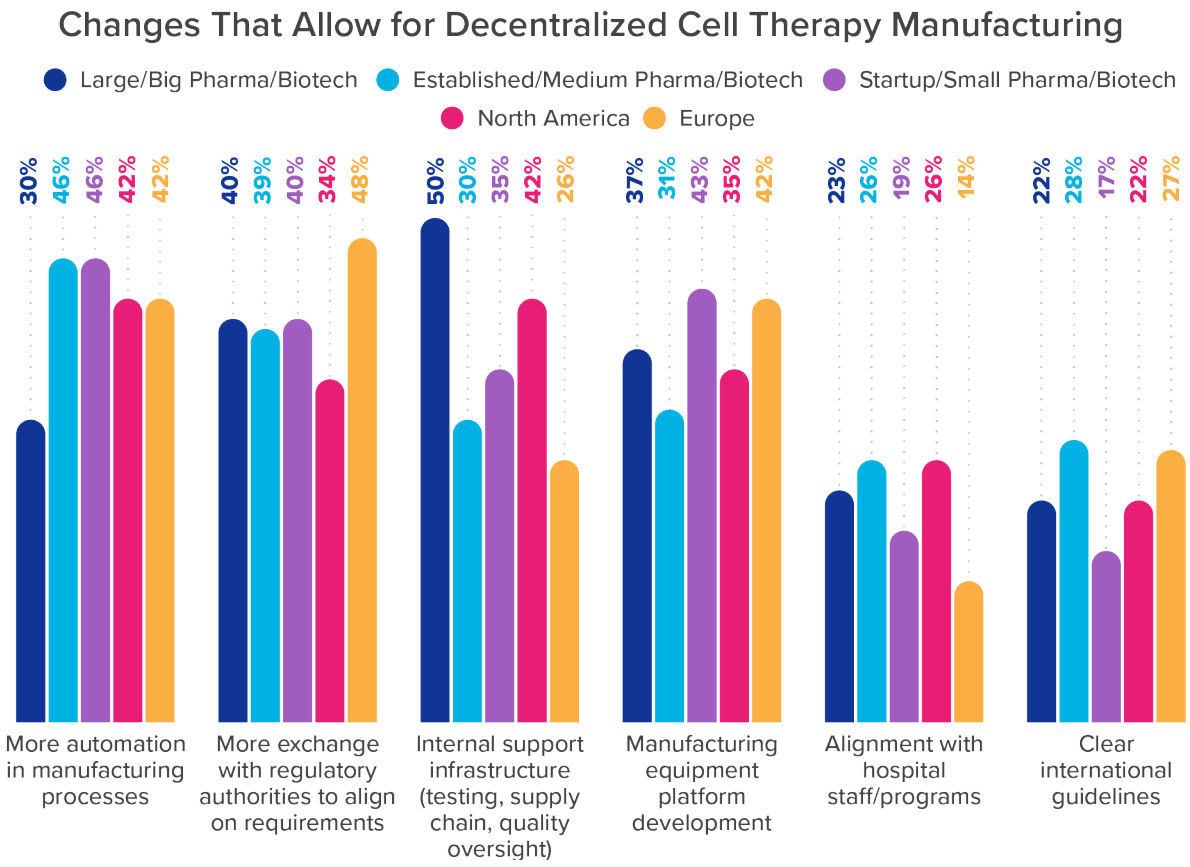
What's behind this preference? In Figure 4.4, a possible answer emerges: European manufacturers are much more likely than those in North America to identify regulatory alignment as the missing piece in a potential future of decentralized manufacturing.

48%

of European manufactures identify regulatory alignment as the most important change needed for decentralized manufacturing

FIGURE 4.4

What are the most important changes needed to allow for decentralized manufacturing for cell therapy?



Source: CRB

Improved harmonization among Europe Member States will go a long way toward addressing this challenge, making decentralized manufacturing more feasible from both a regulatory and a business standpoint.

Respondents from both regions also identified the need for automated processes and a manufacturing equipment platform, which are key to reducing the risk of site-to-site differences as a result of manual operations.

Internal support infrastructure is also important, especially from the perspective of North American companies. It's easy to see why: The more harmonized the training, procedures and overall operations across locations, the better a decentralized approach will work. Operators could move between sites as needed, helping them to rapidly deliver reliable, high-quality therapies made as close as possible to the patient's bedside.

Key Takeaway:

Decentralized manufacturing, while a compelling solution for certain product types, is not a magic bullet. The future of cell therapy manufacturing depends on many solutions, including improved regulatory harmonization and simplified, standardized manufacturing approaches.

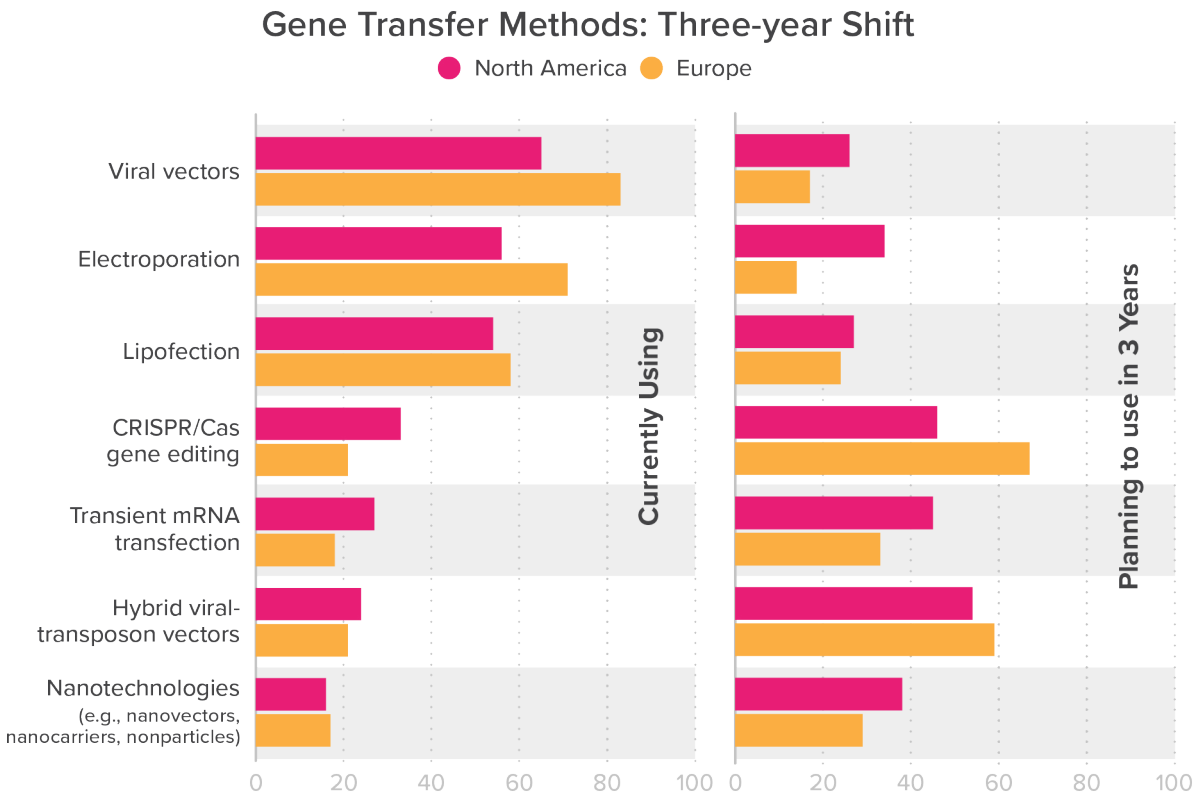
3. GETTING THERAPIES TO MARKET FASTER WITH EMERGING TECHNOLOGIES

Commercial readiness and decentralized manufacturing are both potential accelerants on the road to efficient CGMP manufacturing, but there's a third factor that could have a powerful impact: new gene editing technologies.

Of all the questions we put to our survey respondents from the cell therapy industry, this one painted the clearest picture of where manufacturers plan to go next. Just look at the striking inversion in Figure 4.5: Today's focus on viral vector manufacturing will soon expand to include a future of RNA-based gene editing.

FIGURE 4.5

Which of the following gene transfer methods is your company using or planning to use for cell therapy gene modifications?

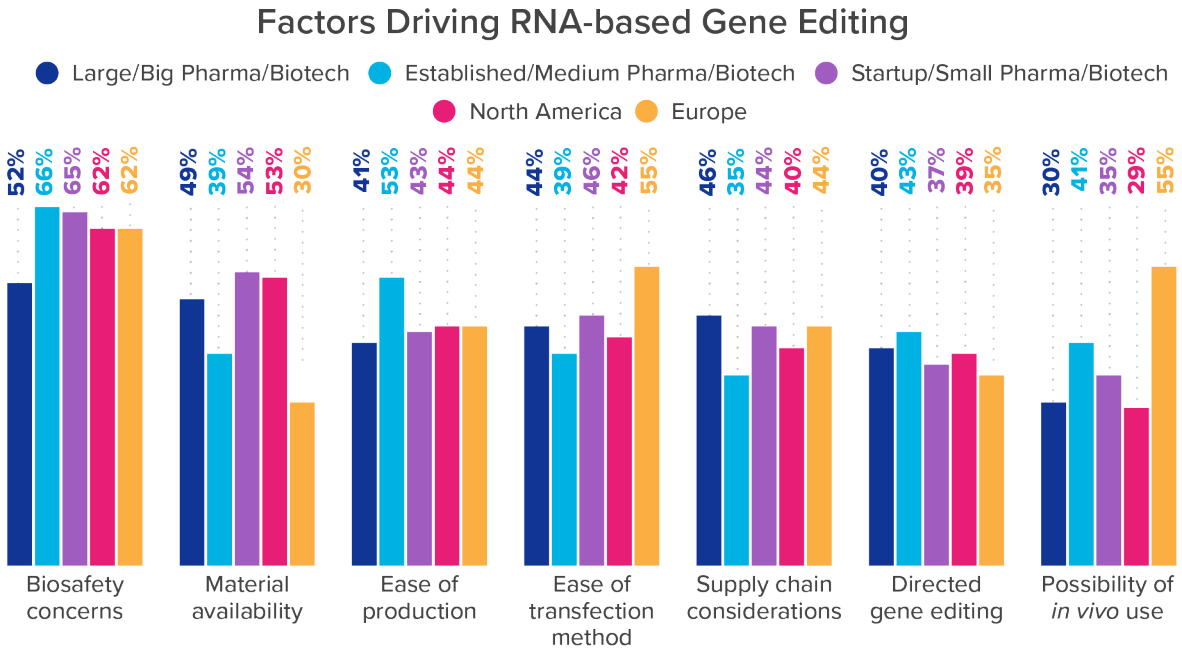


Source: CRB

When we asked about motivations driving this shift, another interesting delta between the North American and European regions emerged (Figure 4.6).

FIGURE 4.6

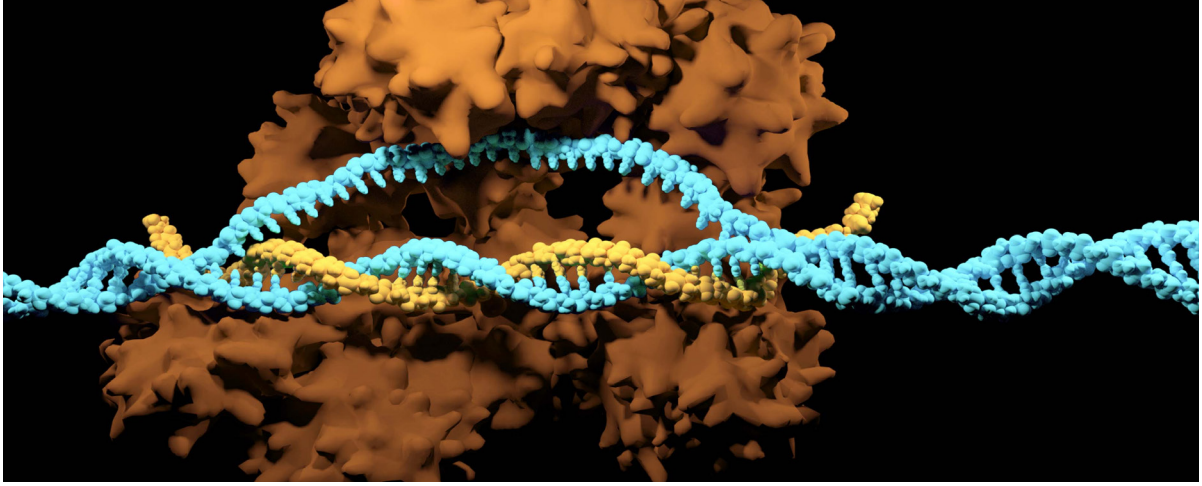
How important are the following factors in your company's plan to use an RNA-based method for gene editing?



Source: CRB

When viruses are no longer part of the manufacturing lifecycle, biosafety concerns diminish—that's a clear driver for respondents who are considering a shift toward RNA-based methods. European manufacturers are also driven by the prospect *in vivo* gene editing supported by targeted genetic modification, which could pave the way for simpler facilities and a smoother regulatory pathway.

Meanwhile, North American companies appear more motivated by material availability concerns than their European counterparts. This could come down to the fact that North American companies seem more inclined toward the large-volume batches typical of *ex vivo* viral-based manufacturing, which may lead to greater supply chain complexity and issues around securing large volumes of certain raw materials.



Key Takeaway:

The world of cell therapies is constantly evolving. First came viral vectors, making these products scientifically possible; now emerging gene editing technologies like CRISPR-Cas9 could make them commercially successful. Manufacturers are watching closely, ready to make the next exciting leap to new platforms.

For patients and manufacturers, cell therapies hold the key to a bright tomorrow

With more than 80% of our survey respondents working in the cell therapy submarket, and a wave of new technologies poised to transform the way these life-saving therapies are produced, the future of cell therapy manufacturing looks bright.

It's not without challenges, though. Today's manufacturers are grappling with the lab-to-commercialization transition and the complexities of moving materials from the bedside to the bench and back again. To address these hurdles, this submarket needs standardized GMP-ready manufacturing platforms supported by a modernized regulatory environment and a willingness to experiment with new manufacturing models such as decentralization.

From what our survey tells us, these solutions are on their way—and they bring the possibility of a stronger, faster, more impactful cell therapy marketplace with them.

From growing fast to growing pains:

Today's gene therapy innovators face new challenges as commercial-scale manufacturing approaches.

By: Peter Walters

Section 5

The gene therapy submarket is in flux. Takeda, Amicus, and other high-profile companies have recently pulled back, and few new entrants appear to be taking their place. According to our survey respondents, this submarket is expected to grow by just 8% over the next three years.

What do these shifts mean for those still in the business of gene therapy production? As the competitive environment contracts, pressure to accelerate development, gain regulatory approval and commercialize production is compounding fast. Meanwhile, an important question hangs in the air: Once a gene therapy reaches the market, who has pockets deep enough to pay for it?

Answering this question will require innovation on multiple fronts, starting with the policies that govern the way life-saving care is compensated. For manufacturers, this brings into focus the upfront resources, time and labor involved in bringing gene therapies to market. New strategies and technologies may help manage those costs, which in turn could impact the price of emerging therapies.

We designed our survey to examine a few of these strategies in action. The result is a close look at three key trends that will shape the future of gene therapies for manufacturers, and for the patients who rely on them.

1. Manufacturers are grappling with whether to pursue established viral-based methods or pivot to a promising new platform.
2. Stable producer cell lines, a critical component of scalable, efficient gene therapy manufacturing, are maturing into clinical use.
3. The contract services marketplace is out of sync with current demand, but that will soon change.

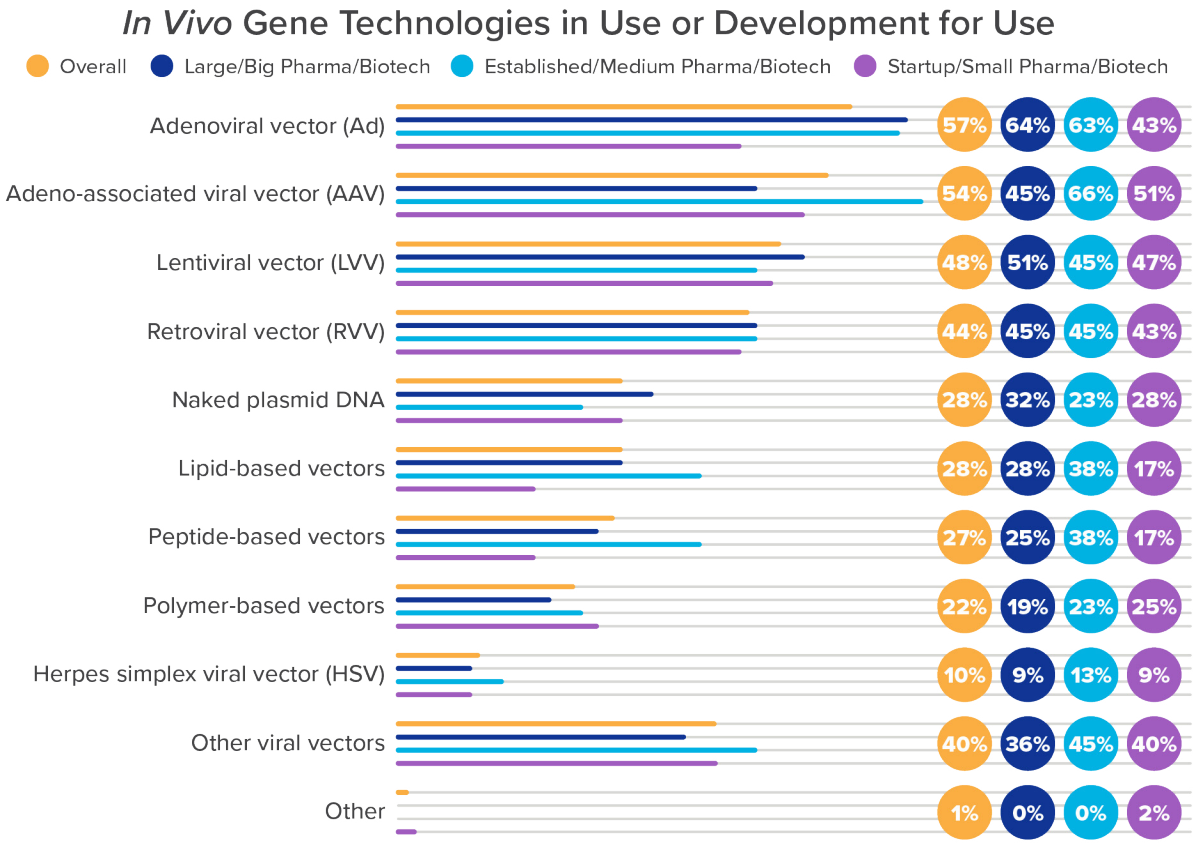
NEW GENE MODIFICATION TECHNOLOGIES ARE ON THE HORIZON

Non-viral manufacturing methods are the minority—but they're gaining momentum

A new paradigm is emerging in the gene therapy zeitgeist. After years spent developing viral-based platforms, this submarket appears to be migrating toward non-viral methods. Likely incentivized by the promise of CRISPR, about a quarter of our respondents plan to develop vectors using lipids, peptides or polymers as opposed to viruses (Figure 5.1).

FIGURE 5.1

Which in vivo gene technologies are your company using/developing for use in CGMP pipeline products within the next three years?



Source: CRB

Through the lens of company sizes, this theory of a “great migration” toward new gene therapy technologies gains some nuance. Medium-sized companies appear most eager to pursue these emerging platforms. Meanwhile, small companies are less likely to have a switch on their horizon, perhaps because they’ve been blazing a trail toward non-viral manufacturing from day one, or because they lack the ability to change course away from an established viral-based platform.

Large companies appear least likely of all to anticipate a pivot away from viral-based manufacturing. Several large firms made record-setting investments in viral vector manufacturing during the industry’s 2021 financial boom; a return on that investment is likely their priority, outweighing the potential long-term benefits of an expensive migration to an unproven, costly new technology platform.

But sunk costs is not the only reason that companies may choose to pursue viral vectors, even as other technologies gain momentum.

Viral methods continue to offer big advantages for those who master their approach

Given that gene therapy manufacturing is a relatively new concept still rife with unknowns, hitching that concept to a well-understood viral-based technology may be a wise choice. For one thing, viral-based platforms have an established reputation among regulating agencies, while bleeding-edge technologies are only just beginning their steep climb toward acceptance.

> ***Viral-based manufacturing: potential impact on patient access and affordability***
>
> *Until emerging non-viral methods mature into commercially viable technologies, viral vectors will likely continue to dominate the gene therapy submarket, which could be good news from a patient access perspective. Developing a gene therapy on the shoulders of an established viral-based process could limit sunk R&D costs, which in turn could translate into a lower sticker price when that therapy reaches the market.*

STABLE PRODUCER CELL LINES ARE MATURING

More than half of manufacturers have moved their stable cell lines from R&D to clinical use

To engineer a lab-scale, viral-based process into a streamlined, CGMP-ready manufacturing operation, developers need to leverage the most scalable technology available. That almost always means implementing a stable producer cell line—a challenge to develop, but a must-have from the perspective of manufacturing efficiency and, ultimately, patient accessibility.

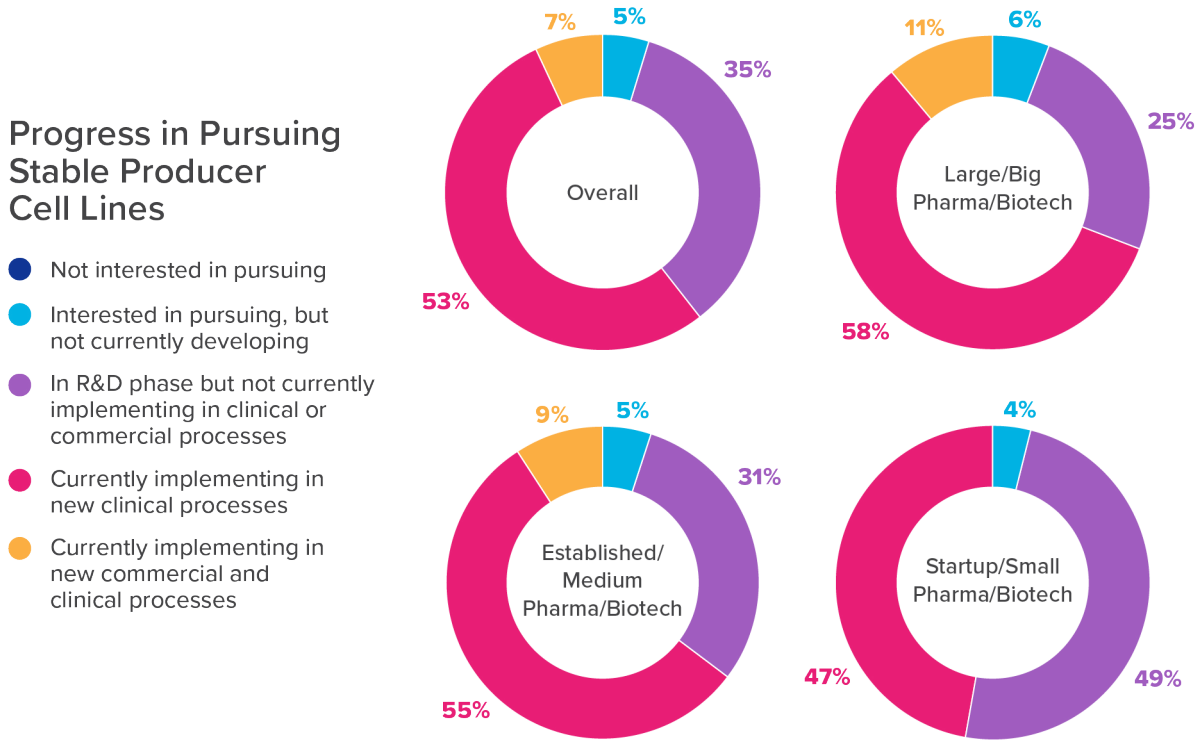
In contrast to a more conventional cell line, which requires manufacturers to grow a culture to production volume before transfection, stable producer cell lines offer a simpler, more streamlined process. Cells are stably transfected at the cell bank level; as they reproduce, they replicate to future generations their modified genome. This

approach lowers raw material costs, reduces unit operations and typically increases scalable production yields. For those reasons, a stable producer cell line is a key to the kingdom of efficient viral-based gene therapy manufacturing.

This is likely why 95% of our survey respondents are pursuing stable producer cell lines, and 60% have reached the point of using stable producer cells in their clinical or commercial process (Figure 5.2).

FIGURE 5.2

What progress has your company made in pursuing stable producer cell lines for CGMP viral vector manufacturing?



Source: CRB

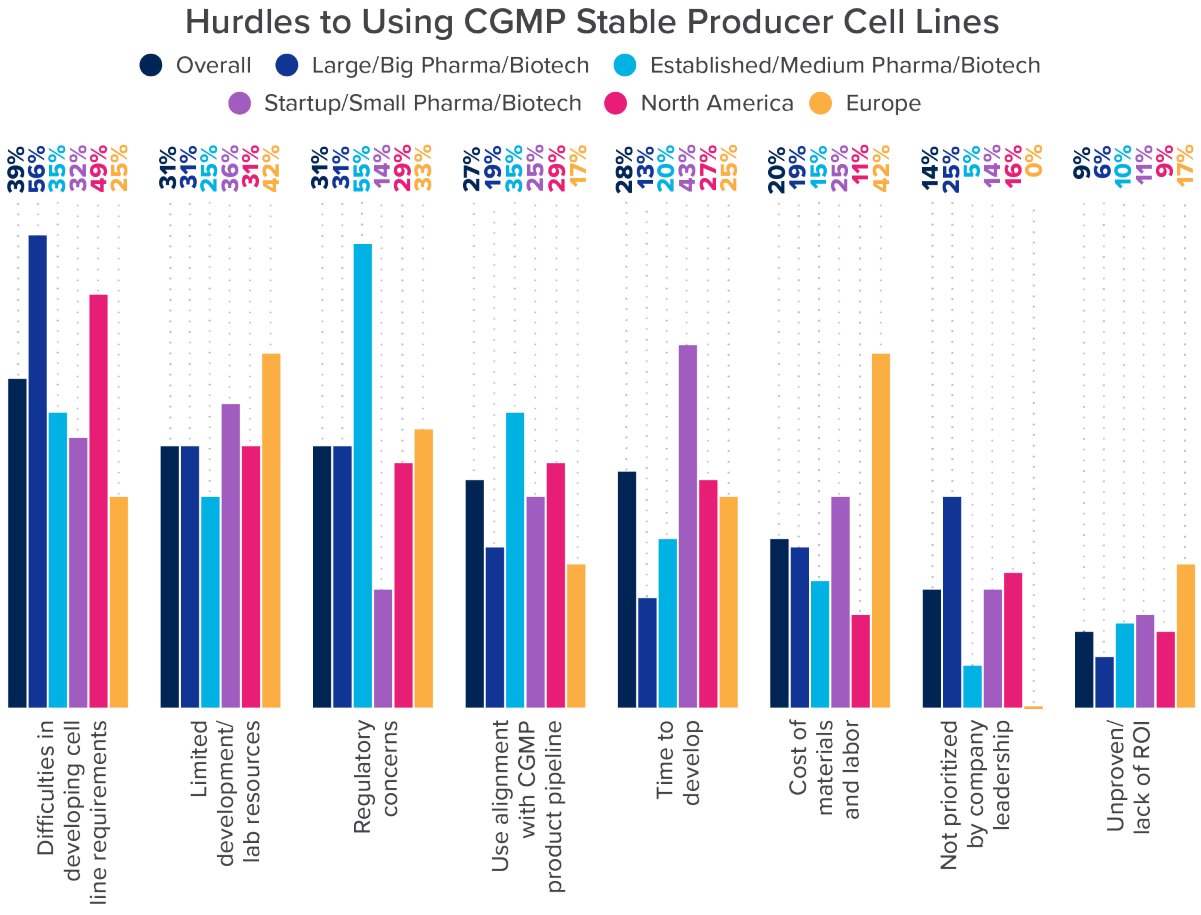
For those still developing stable producer cell lines, the road ahead could be challenging

Despite the growing maturity of this technology, 35% of respondents are still striving to move it out of the R&D phase. Small companies appear especially vulnerable to being left behind, while medium and large companies are sprinting ahead.

To understand the full scope of this challenge, we asked respondents about the hurdles they face on their way to establishing their stable producer cell line. Unsurprisingly, most companies are chiefly concerned with the development process itself. Developing a stable cell line is notoriously difficult and requires significant upfront resources, time, materials and labor—a compounding challenge that we see reflected all the way down Figure 5.3.

FIGURE 5.3

What are your company's two biggest hurdles to actualizing the use of CGMP stable producer cell lines?



Source: CRB

Licensing is a popular solution—but it introduces its own risks

Many manufacturers have a strategy for overcoming the challenge of developing a stable cell line: Leave it to someone else. This is an especially popular approach in Europe, where 53% of respondents license proprietary host cell lines (for a closer look at these numbers, see Figure 5.4 in the next section). This could explain why

only 25% of respondents from Europe appear concerned about development difficulties, compared to 49% from North America.

The advantages of leapfrogging development hold great appeal for startups, too—more than half appear committed to this strategy. And why not? By licensing a third party's stable producer cell line, companies can potentially eliminate many upfront costs and delays, accelerate the approval process, and position themselves for a smoother pathway to commercial-scale CGMP production.

This strategy does introduce considerable risk, though. When they sign that licensing deal, manufacturers relinquish at least some control over a key component of their manufacturing platform, which could leave them vulnerable.

Given these considerations, should manufacturers take the time to develop a proprietary stable cell line in-house, or accelerate speed-to-market by licensing one from a contractor? Each company must answer this question for themselves, based on their business goals and their perception of the benefits and risks that line each pathway.

> ***Stable cell lines: potential impact on patient access and affordability***
>
> *By laying the groundwork for a much more efficient and scalable CGMP manufacturing process, stable producer cell lines could ultimately help lower the cost facing patients.*

CONTRACT ORGANIZATIONS ARE NOT IN SYNC WITH CURRENT DEMAND

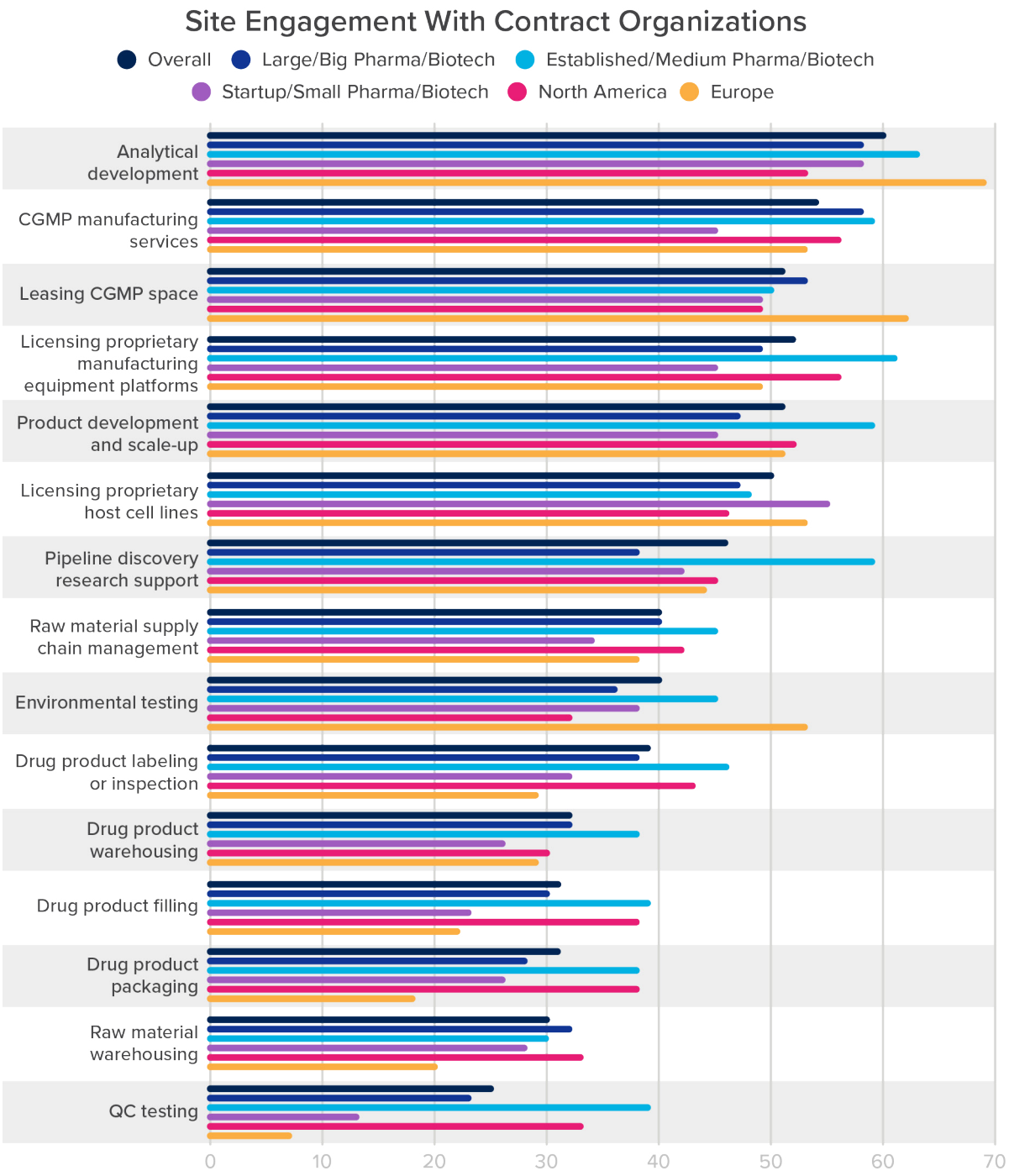
Gene therapy manufacturers rely on contracting as a key part of their business model

In some ways, today's maturing gene therapy submarket mirrors the early days of monoclonal antibody (mAb) development, when technologies that are now commonplace were novel, expensive and not yet well understood. But there is something that gene therapy manufacturers have which those early mAb pioneers did not: a thriving marketplace of contracted services.

With so much tailored support available, gene therapy manufacturers can piece together a manufacturing operation without developing every last capability in-house. As a result, they have come to rely heavily on contracted services, often to a far greater degree than companies in other submarkets. Fifty-four percent of gene therapy respondents engage contractors for CGMP manufacturing services, for example, compared to just 34% across the life science industry as a whole (Figure 5.4).

FIGURE 5.4

Is your site engaging with contract organizations to support your CGMP gene therapy pipeline delivery in any of the following ways?



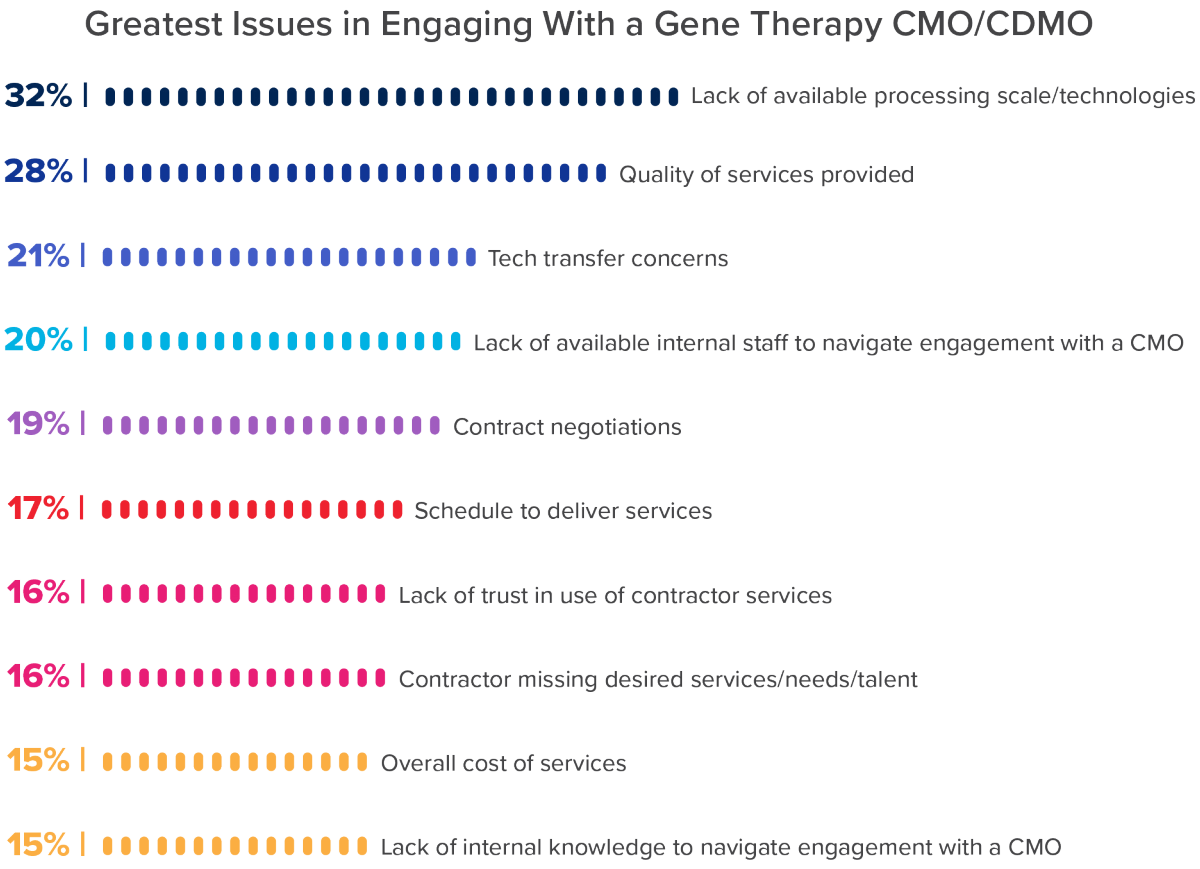
Source: CRB

The market for contracted services is oversaturated—for now

Seeing opportunity in this trend, companies and investors rushed to launch gene therapy-related contracted services over recent years. A "shadow" industry has emerged as a result—one tailored to meet the needs of an underserved market, though not always well. Gene therapy manufacturers often face a lack of available technologies and poor quality when working with contractors, according to our survey (Figure 5.5). More than a third of these manufacturers also perceive that the contracted services market has outpaced demand (Figure 5.6).

FIGURE 5.5

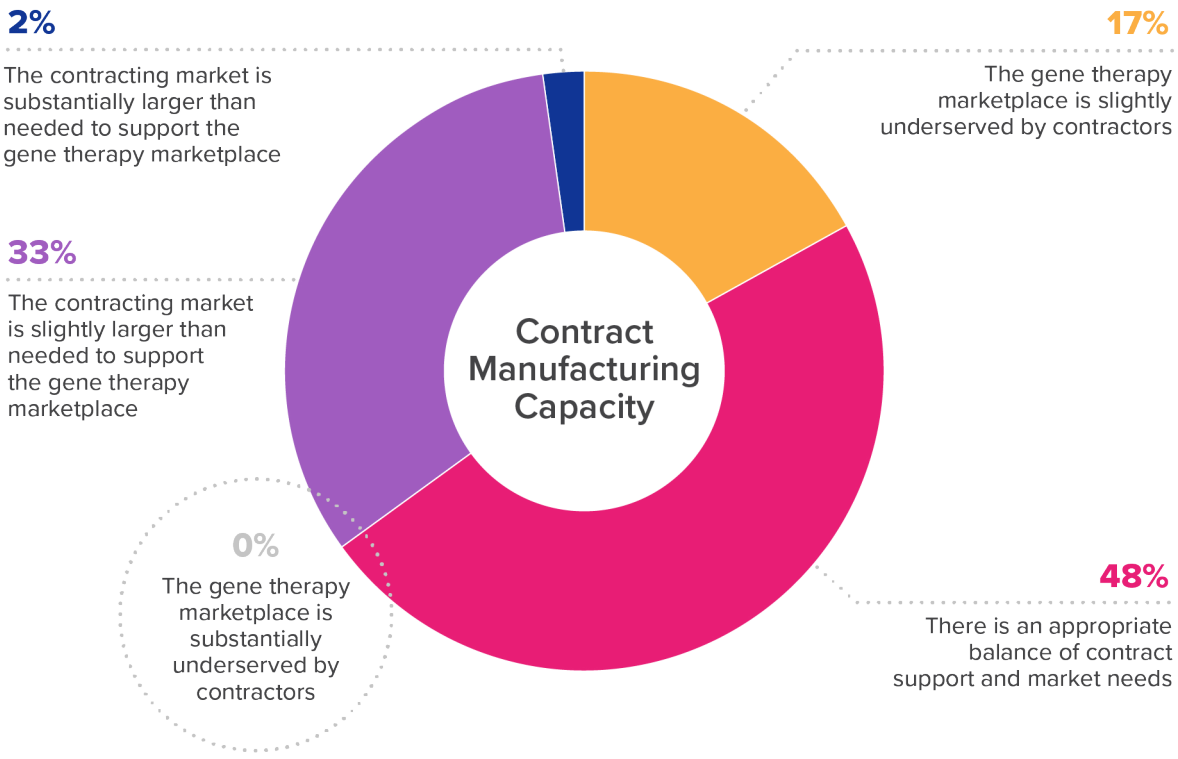
What are your site's two greatest issues in engaging with a gene therapy CMO/CDMO?



Source: CRB

FIGURE 5.6

In your opinion, how much contract manufacturing capacity is there for the need in the gene therapy market?



Source: CRB

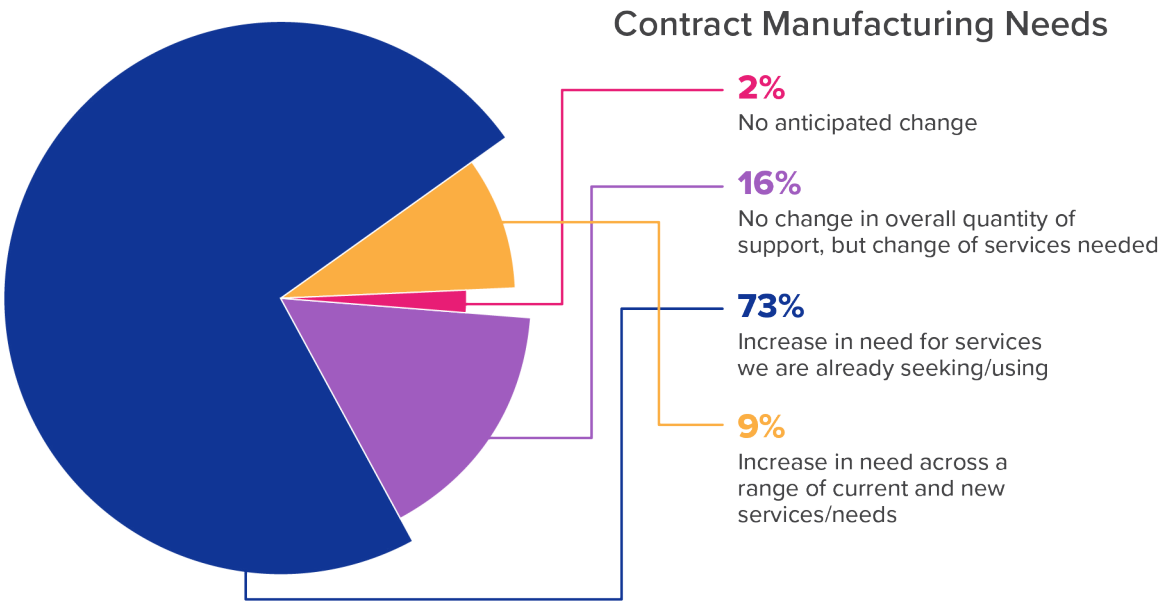
Together, these survey results suggest a problematic situation: the contracted services market may be underperforming, and now it could be on the verge of becoming overcrowded, as well.

What's next for contracted services in the gene therapy sub-market?

This mismatch between supply and demand in the contracted services market isn't only down to ballooning contractor capacity. It's also a product of how gene therapy manufacturers use contracted services. It appears that the era of urgent demand for all-new services is tapering off; as today's manufacturers progress through clinical phases and approach commercial-scale manufacturing, what they will need over the next three years is more of what they already have (Figure 5.7).

FIGURE 5.7

Do you anticipate your site's contracting needs to increase over the next three years?



Source: CRB

If you're a contractor in this sub-market, this could be good news. Your short-term challenge is to survive in an overcrowded marketplace; in the long-term, your resilience could be rewarded when gene therapy manufacturers scale up demand for existing services and you're still here to meet that need.

On the project owner's side, these survey results emphasize the importance of due diligence when selecting a contracted services provider. If you're likely to stay with this partner for the long-term, scaling your existing services as you grow, then you need a partner capable of growing with you—and who won't confront you with any of the challenges reported in Figure 5.5.

CMO/project owner relationships: potential impact on patient access and affordability

CMO partnership is a key strategy for accelerating gene therapies to market, and the right relationship could reduce manufacturers' R&D time, staffing and startup—which in turn could positively impact patient access.

The cost of a cure

Some of today's gene therapy companies are transitioning away from the space. Others are either staying put and doubling down on a viral-based platform or investing in moonshot technologies that could shape the long-term future of gene therapy manufacturing.

Whatever their choice, each company must consider not just the risks and rewards lining their pathway to commercial-scale manufacturing, but also—and most importantly—the patients waiting at the end of that pathway. Supporting greater access to life-saving therapies is the driving force behind today's evolving gene therapy landscape.

Better, faster, cleaner:
Antibody-drug conjugates take their place among fast-growing modalities

By: Ashley Harp

Section 6

Many believe we've entered a golden age for medicine. From CAR-T cell therapies that treat childhood leukemia to the application of CRISPR gene therapy to treat sickle cell disease, it's easy to see why. Among these novel drugs are antibody-drug conjugates (ADCs), which are showing great promise in treating blood cancers and solid tumors, including breast, ovarian and cervical cancers. ADCs are a growing class of biologics embraced by 35% of all life sciences experts we surveyed who said their company's site develops or manufactures them. This number is much lower than those involved with monoclonal antibodies (mAb) and cell and gene therapies, but is expected to grow to 43% within three years. We aren't surprised by this growth—while there are only 13 FDA-approved ADCs currently on the market, there were more than 500 in pre-clinical studies and more than 200 in clinical studies as of 2022.

Making ADCs relies on large volumes of solvents, creates hazardous waste and has a high risk of cross-contamination. It's also more complex than for most other biologics and generally includes:

- Payload/linker synthesis
- mAb manufacturing and purification
- mAb and modification/reduction and purification
- Conjugation of a highly potent payload, linker and the reduced mAb
- Conjugate purification
- Lyophilization upon completion of filling

We asked respondents whose companies are involved with ADCs for their take on the challenges of manufacturing these targeted therapeutics.

Key Takeaways:

- *Companies are focusing on their waste streams, demonstrating the importance of sustainability efforts even in high-margin processes.*
- *New purification technologies are being adopted to reduce liquid waste, use less material and reduce processing time.*
- *Cytotoxicity is increasing, requiring enhanced focus on safety for development & manufacturing facilities.*
- *Stainless steel continues to be important, likely because of safety concerns about compound toxicity.*
- *Regulations are largely sufficient, with minor clarifications needed.*

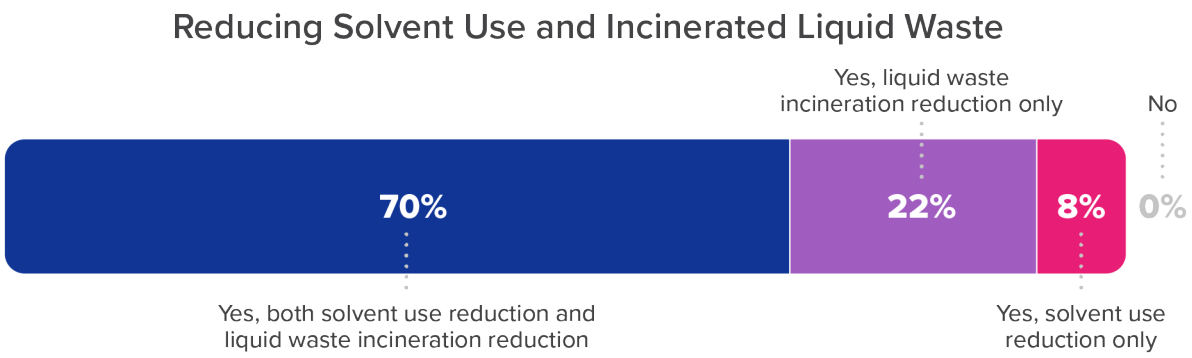
MOST HAVE A PLAN TO REDUCE SOLVENT USE

Heavy solvent use occurs during synthesis and, to a lesser extent, during conjugation. For example, a conjugation reaction requiring a 200 L vessel, uses roughly 10–30 L of solvent per kg of ADC. Synthesis, on the other hand, requires hundreds of liters of solvent per kg of drug-linker.

Virtually all respondents said their companies have a plan in place to reduce solvent use and/or incinerated liquid waste within five years (Figure 6.1). We find this level of engagement encouraging. Given that our respondents skewed toward in-house manufacturing (i.e., few CDMOs), companies appear to be taking their sustainability goals seriously and expect their CDMO partners to do the same.

FIGURE 6.1

Does your company have a plan in place for reducing solvent use and/or incinerated liquid waste in the next five years?



Source: CRB

Continuous chromatography can significantly reduce solvent use

To achieve these goals, producers will require technological advancements for waste treatment, as well as make changes to reduce the number of solvents and buffers used during production. Continuous chromatography technology has the potential to reduce solvent use during drug and drug-linker synthesis, as well as conjugate purification, which would be a huge win for the industry. Most respondents (82%) indicated their site was considering adding continuous chromatography during synthesis within five years. Bachem has proven the commercial viability of continuous chromatography in the oligonucleotide manufacturing process with at least a 30% reduction of solvent use.

For those aiming to implement these reductions soon—even within the next 10 years—changes need to begin today in process development and product development labs. We estimate it will take at least five years to develop and optimize the process, with an additional five years to design, build and qualify a manufacturing facility project.

Solvents used to conjugate drug-linkers

The most commonly used solvents during drug-linker conjugation at commercial scale have been dimethyl sulfoxide (DMSO) and N,N-dimethylacetamide (DMA). We were surprised that the two most popular solvents used right now are ethanol (by 87%) and methanol (by 77%) (Figure 6.2), flammable solvents that require complex design and facility safeguards when used at large scale but may reflect the high percentage of molecules in the clinic. The data indicates a future increase in reliance on DMSO and DMA, which could reflect the expectation that more ADCs will enter commercial manufacturing. DMSO and DMA are combustible liquids, requiring lower levels of facility and equipment protection when compared to ethanol and methanol. They do, however, come with their own unique challenges. For example, materials dissolved in DMSO are more easily absorbed through the skin, creating a greater hazard for operators.

results indicate that the two most popular solvents are

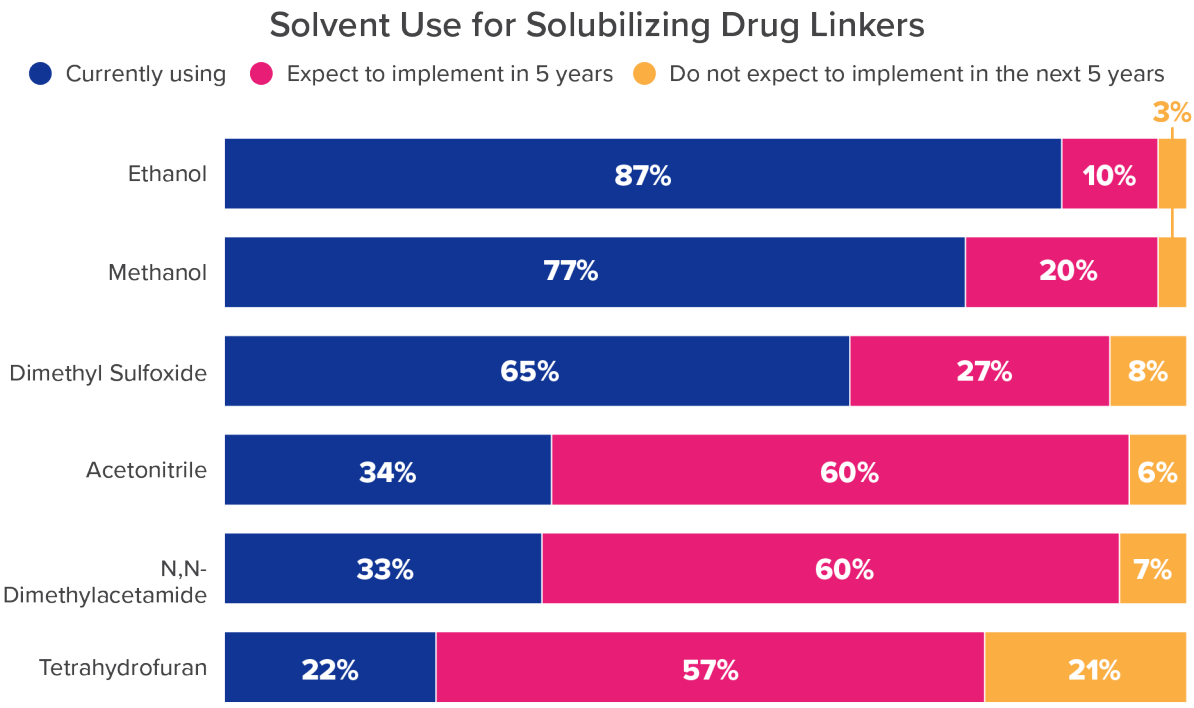
ethanol & methanol

The significant increase in expected use of acetonitrile (ACN) and tetrahydrofuran (THF) may reflect the expected need to overcome increased hydrophobicity. To avoid increased facility, equipment and operating costs, process development will be needed to minimize the use of these hazardous and flammable solvents.

We did not include N,N'-Dimethylformamide (DMF) in this survey due to its environmental and health hazards.

FIGURE 6.2

What solvents does your site currently use or expect to use for solubilizing your drug-linker in the next five years?



Source: CRB

SAFETY FRONT AND CENTER AS CYTOTOXICITY INCREASES

The highly toxic nature of ADCs presents unique manufacturing challenges, which increases alongside the toxicity of payloads. As ADCs evolve, manufacturers need to address these risks through facility design, equipment innovations and cleaning protocols.

Higher containment levels are expected

The occupational exposure limit (OEL) is the degree of exposure to a hazardous chemical for a specified length of time (usually eight hours) that is unlikely to harm a worker.

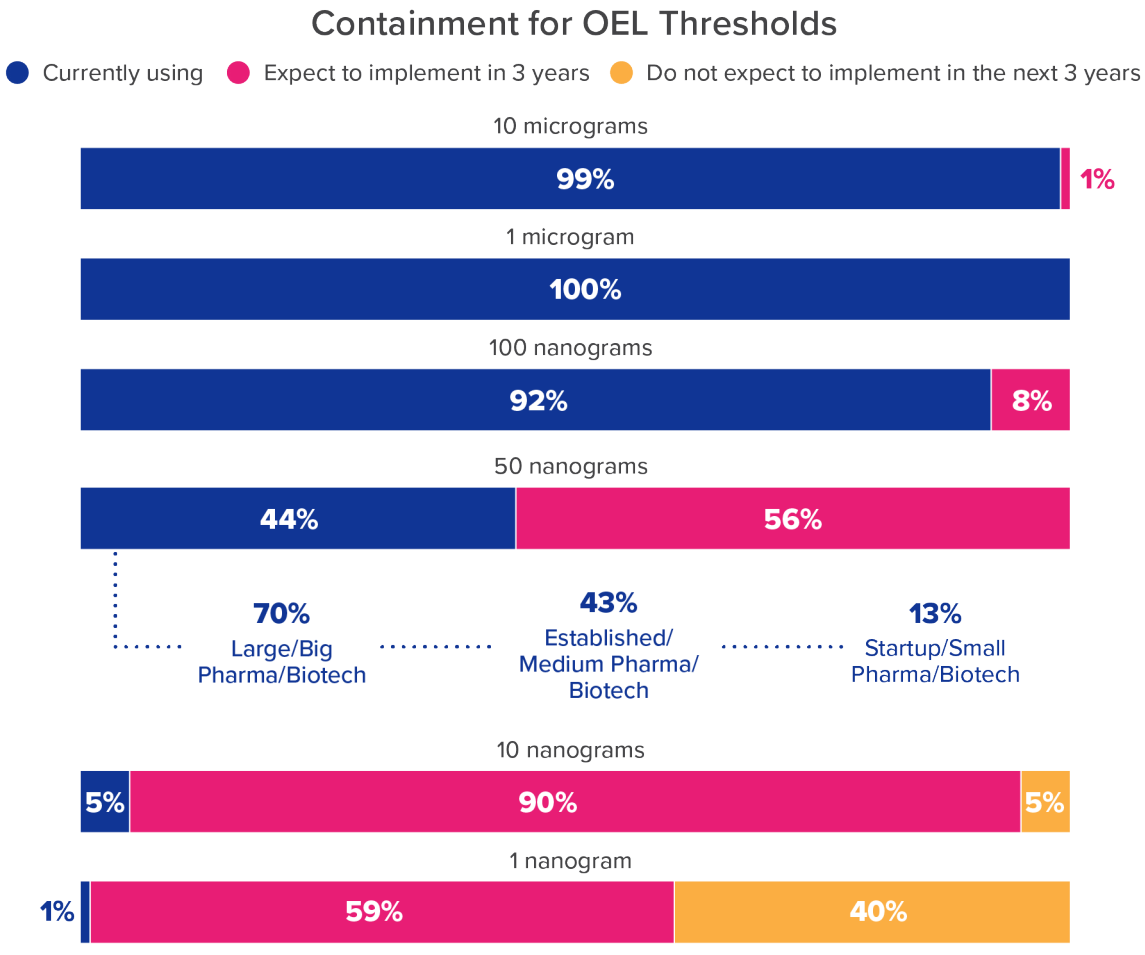
There was a general expectation that OELs will be much lower within the next three years. Everyone surveyed expected to be able to handle an OEL of 50 ng, while 95% intended to go as low as 10 ng (Figure 6.3). We've been hearing from equipment manufacturers that the request for OEL thresholds as low as 1 ng is on the rise, and while only 1% of respondents said they currently use such a low OEL, an additional 59% expect to implement it within three years.

Many more respondents from large pharma companies indicated that they currently use an OEL threshold of 50 ng (70%) than do startups and small companies (13%). This may be due to a lack of internal capability on the part of startups to handle such toxic compounds.

We know that safety must be foundational for development and manufacturing facilities as toxicity is driving higher. This makes the industrial hygienist an essential team member, with risk assessments a critical part of the design process of both the product and the facility.

FIGURE 6.3

What containment for OEL thresholds does your site currently use or expect to implement in the next three years?



Source: CRB

To meet a desired OEL, containment strategies, along with confirmation of their effectiveness, must be put in place to minimize health hazards, environmental risks and cross-contamination during unit operations involving the drug, drug-linker and ADC.

The containment strategy typically incorporates three levels of control:

- Engineering controls, including equipment design, closed product handling and transfers, as well as facility design
- Personal protective equipment (PPE) and gowning protocols
- Administrative controls, including operating procedures, batch scheduling, SOPs, training and limiting the time that operators spend in areas where exposure to drug, drug-linker or an ADC is possible

NEWER PURIFICATION METHODS ARE REDUCING BUFFER USE

The first step in many traditional ADC processes following conjugation relies on tangential flow filtration (TFF) of the assembled ADCs to remove solvents, reagents and excess drug-linker, as well as concentrate the drug substance for further purification or use. Further purification removes unconjugated mAbs, ADCs with an incorrect drug-antibody ratio (DAR) and aggregated ADCs.

Sites intend to continue using traditional purification methods like size exclusion chromatography (47%) and hydrophobic interaction chromatography (47%) (Figure 6.4). Those in Europe were more likely to say they plan to add membrane filtration and size exclusion chromatography than their North American counterparts (Figure 6.4).

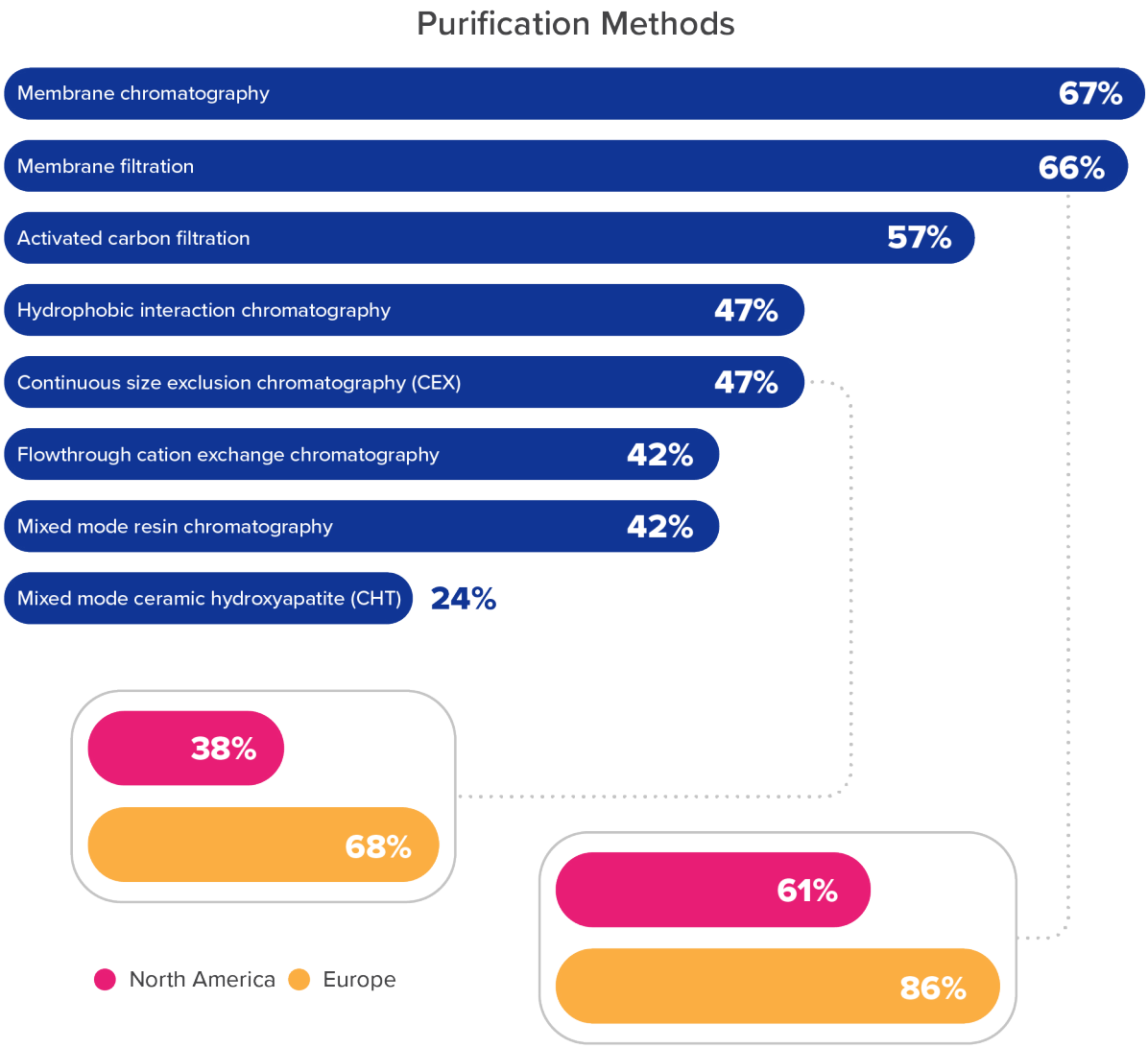
Instead of relying solely on TFF buffers to remove solvents, significant numbers of respondents said their sites will soon be using purification methods that are new to commercial-scale manufacturing, including:

- Membrane chromatography (67%), which is useful for aggregate removal, DAR separation, endotoxin removal and novel payloads
- Membrane filtration (66%)
- Activated carbon filtration (57%), which can be used for novel payload removal as well as unusual side product removal followed by TFF

Improving purification processes is a key way for facilities to reduce the volume of buffers. In addition to reducing liquid waste, these methods use less raw material and reduce process time.

FIGURE 6.4

Is your site planning to implement the following ADC purification methods in the next five years?



Source: CRB

MOST SITES PLAN TO ADD SPRAY DRYERS WITHIN FIVE YEARS

Lyophilization is most commonly used to provide long-term stability for protein-based biopharmaceuticals, like ADCs. Spray drying, which is currently used for drugs that rely on large-scale continuous processes, such as oral solid dose (OSD) and inhalable drugs, improves bioavailability and offers a more efficient and cost-effective alternative, with shorter time required to achieve stable product.

We were surprised to learn that 83% of respondents said their site was planning to use spray dryers within five years. Spray dryers can be difficult to clean and require increased handling of parts contaminated with cytotoxics compared to lyophilization equipment. Most of those who work with mRNA also expect to see the use of aseptic spray dryers for their products within five years (Figure 3.5), suggesting a potential industry-wide shift to this technology.

Safety precautions will need to improve

If ADC manufacturers intend to use spray dryers as widely as this data suggests, there will need to be equipment design improvements so they can safely handle increasingly toxic drugs in powder form. Although there are spray dryers on the market capable of aseptic manufacturing with low OEL containment, they're not fully cleanable without being opened. In addition, most of the industry's fill-finish capacity relies on liquid filling and integration with lyophilizers. Transitioning to spray-dried, powder-based filling is possible but requires a commitment to industry disruption and advances in equipment technology.

STAINLESS STEEL IS STILL USED, ESPECIALLY FOR BUFFER PREP AND STORAGE

We see that most ADC producers use only single-use technology (SUT) for mAb reduction (71%) and for purification of reduced mAbs (55%) (Figure 6.5). This is understandable given the general shift among mAb manufacturers toward SUT. Interestingly, there was a great disparity between the embrace of SUT for mAb reduction in North America (82%) and Europe (45%).

The numbers are lower for SUT in conjugation (35%) and final purification (30%). In terms of conjugation, there are reasons stainless steel (SS) may be preferred; for example:

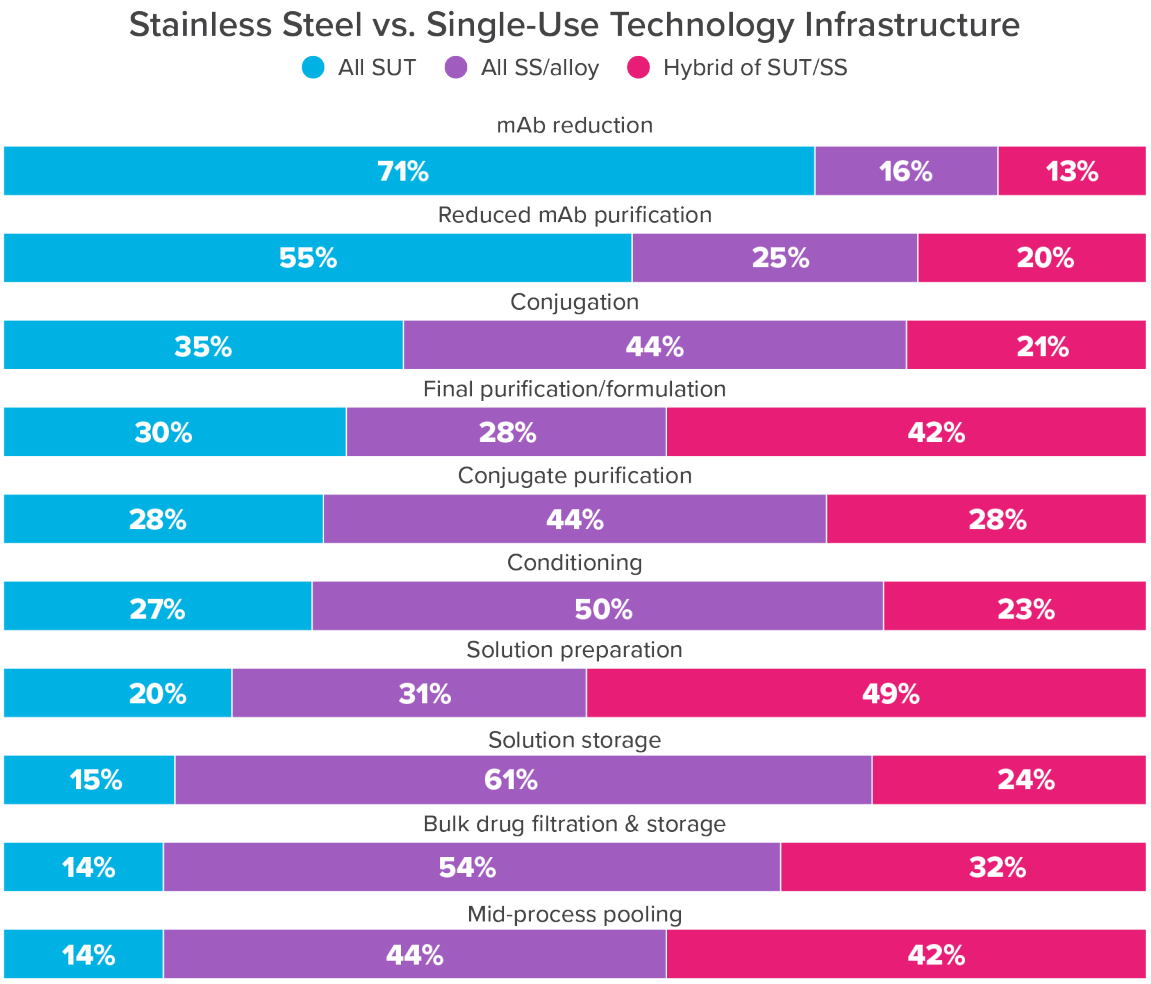
- At sites that use only one drug-linker to produce one ADC, which eliminates the risk of cross-contamination of different drug-linkers
- To meet more stringent building codes necessary where flammable solvents are used (e.g., ethanol, methanol)
- To address compatibility concerns with the various drug-linker dissolution solvents
- To reduce ongoing operating costs

Given that mAb producers have also largely migrated to SUT for buffer solution preparation and storage—in part to reduce the need for clean-in-place (CIP)—it surprised us that many ADC manufacturers indicated they were using only SS or a combination of SS and SUT for buffer prep (80%) and buffer storage (85%). Perhaps this is due to the lack of HPAPIs in these buffers, meaning that cleaning can use standard CIP processes without generating additional solid waste and solvent waste.

Liquid waste may also be treated as standard process waste from these steps, so cleaning solutions do not add to the incineration load. Over the long term there are likely cost savings to using stainless steel for buffer preparation and storage.

FIGURE 6.5

Where does your organization primarily leverage single-use technology (SUT), stainless steel (SS) or higher alloy infrastructure, or a hybrid of SUT and SS technology to manufacture ADCs?



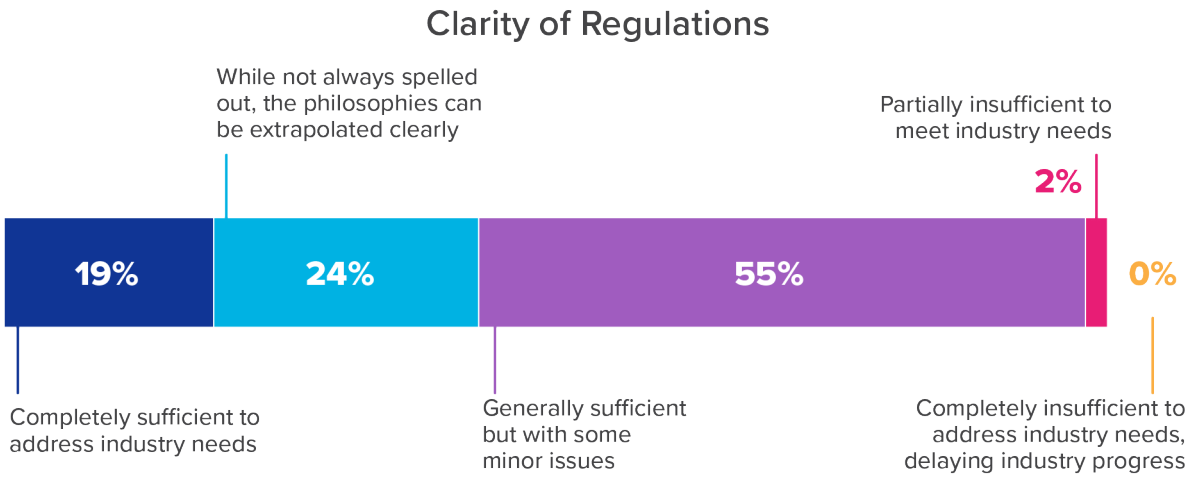
Source: CRB

MINOR REGULATORY ISSUES NEED TO BE RESOLVED

Almost all respondents (98%) said the current global regulations concerning ADCs are at least sufficient (Figure 6.6). The regulatory guidance for each component is sufficient. The questions arise when all those components are brought together and there are regulatory issues that need to be addressed.

FIGURE 6.6

How clear are current global regulations regarding ADCs?



Source: CRB

The need to work with regulators

Manufacturing ADCs is considerably different from mAbs, for which standardized processes and regulatory guidance are clear. The question of how to file ADCs is unclear. Should they be filed as drugs or as therapeutic proteins? Should you follow regulations for therapeutic proteins or for HPAPI compounds? Currently, you may follow either or, more conservatively, both.

This makes it critical for manufacturers to confirm that their plans and strategies are acceptable to regulators. Unlike a mAb facility, most audits can't occur in production spaces with exposure hazards. This means facility design should include viewing corridors or other ways to observe manufacturing spaces.

Improved manufacturing will bring more potent medicines

ADC manufacturing is maturing, spurred by a desire to improve bioavailability for patients, reduce liquid waste, ensure the safety of workers and reduce the risk of cross-contamination as cytotoxicity increases. Improved manufacturing techniques, equipment capabilities and process knowledge are critical to ensure this maturation continues. Close collaboration across the industry will ensure treatments are not delayed for this critical patient population as manufacturing challenges arise and technical advancements appear.

All roads lead to Drug Product:

Product type, regulations and new technologies are driving innovation in the production space.

By: Luke Stockhausen

Section 7

Looking at the lifecycle of drug therapy manufacturing, drug products are the final form that find their way to the patient. This is the last stop at which quality and manufacturing excellence intersect to put the product in its final container and dosage form for the patient. It is essential to have a roadmap of what's ahead for products and therapies to accurately predict the impacts on process, equipment and facility design. As the markets for products across all modalities inevitably progress, aseptic and sterile product facilities, equipment, packaging and regulatory oversight must adapt to meet patient needs safely and efficiently.

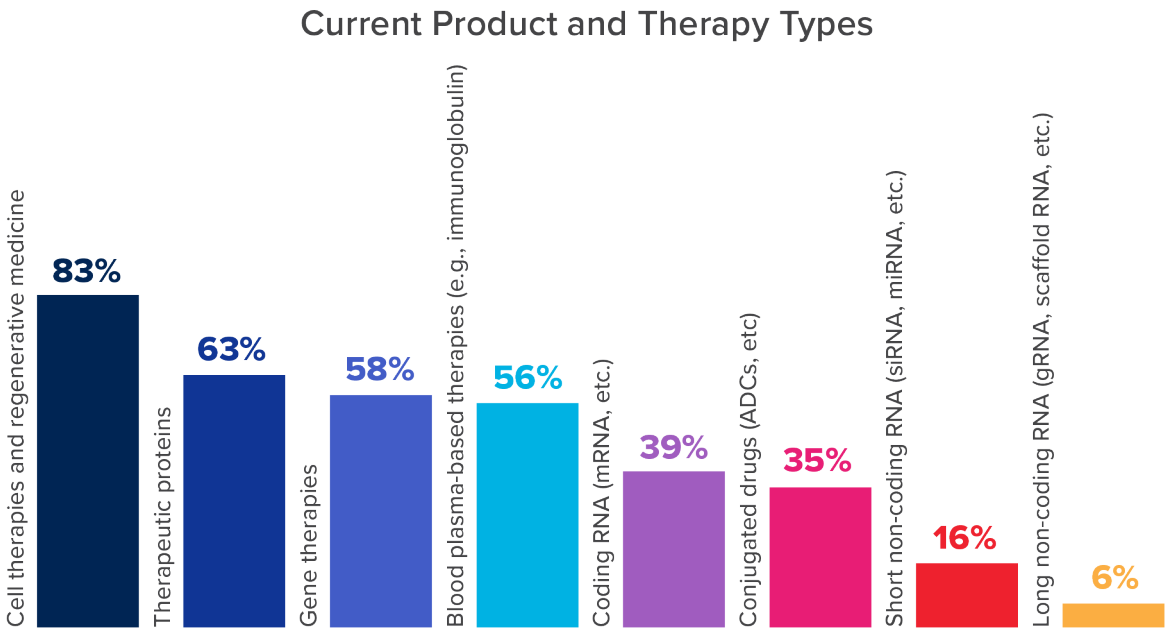
This section of *Horizons* offers an overview of the influences of individual product and therapy types on production and explores the regulatory environment, with a particular focus on EudraLex Annex 1. Finally, it reviews the results of data gathered on cryogenics, container types and batch sizes, and what these may mean for facility design moving forward.

THE IMPACTS OF PRODUCT TYPE ON PRODUCTION

Our survey respondents are planning for growth across all categories. Each modality, and many times, each product, has variations that lead to different container needs, equipment design and facility requirements.

FIGURE 7.1

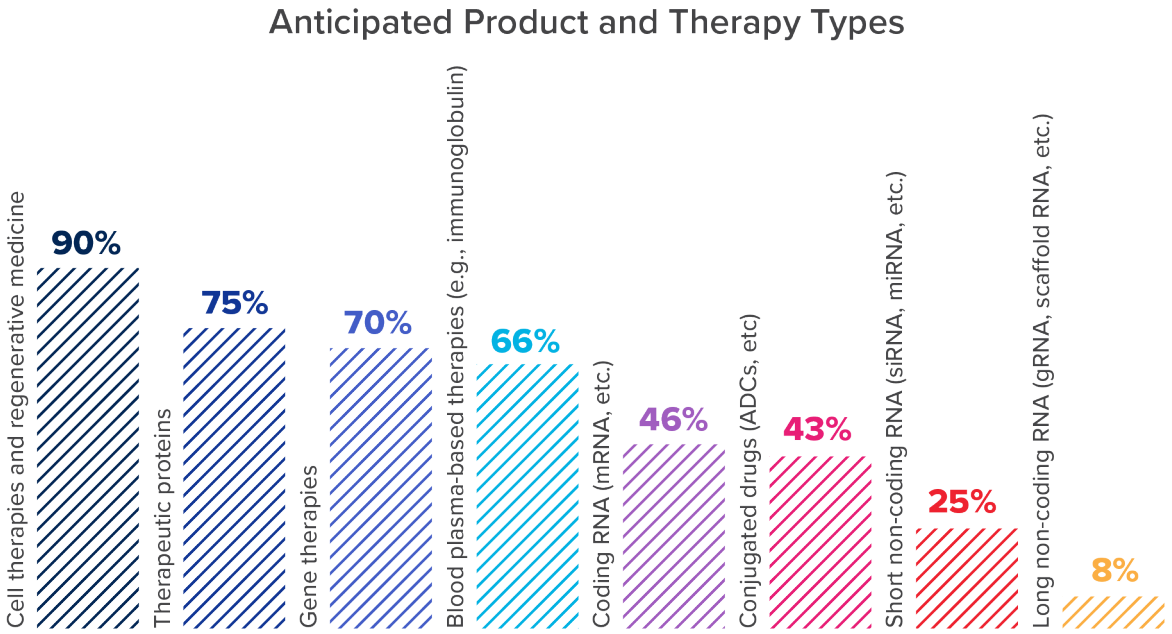
What product types are your company's site currently developing and/or manufacturing?



Source: CRB

FIGURE 7.2

What therapy types does your company's site anticipate developing in your product pipeline within the next three years?



Source: CRB

- Plasma-based products are usually large-volume parenterals (bags) and are sensitive to shear. As immunoglobulin G and albumin are being used for new indications or to support delicate patients, the processes downstream of filling create complex facility design and throughput considerations along with supply chain and distribution complexities.
- The cell therapy and gene therapy markets are changing every year, and the drug product space in these areas is evolving rapidly to meet these shifts. Smaller fillers, cold chain requirements, timing from processing back to the patient and complex aseptic processing steps drive the design of the equipment, the container and the facility. Even the location of the facility becomes important to allow for faster delivery of therapy to the patient.
- Conjugate drug products are changing more rapidly now than ever before, and the linker manufacturing as a stand-alone business is changing how conjugation occurs. Expect to see more products that are conjugates. Some antibody-drug conjugates (ADCs) have potent compounds associated with them which create distinct facility and equipment challenges.
- Biological therapeutics, including monoclonal antibodies (mAbs), are continuing to grow and create blockbuster indications for wide-ranging therapies.
- Small molecule products cannot be left out of this discussion. There are more of these products hitting the market to serve medium and large populations. Small molecule products are often more stable and can be processed in simpler systems. What's more, some of them can be lyophilized, which will improve efficiencies in shipping and storage.
- Aging facilities and new regulatory environments also toggle the market. New regulations will affect throughput and capacity in some instances. Many companies will need to do realignments to produce products in a safe and compliant manner. Some of these changes will open up new opportunities for suppliers. And some orphan drugs and products on the drug shortage list must be monitored closely to make sure that disruptions do not occur.

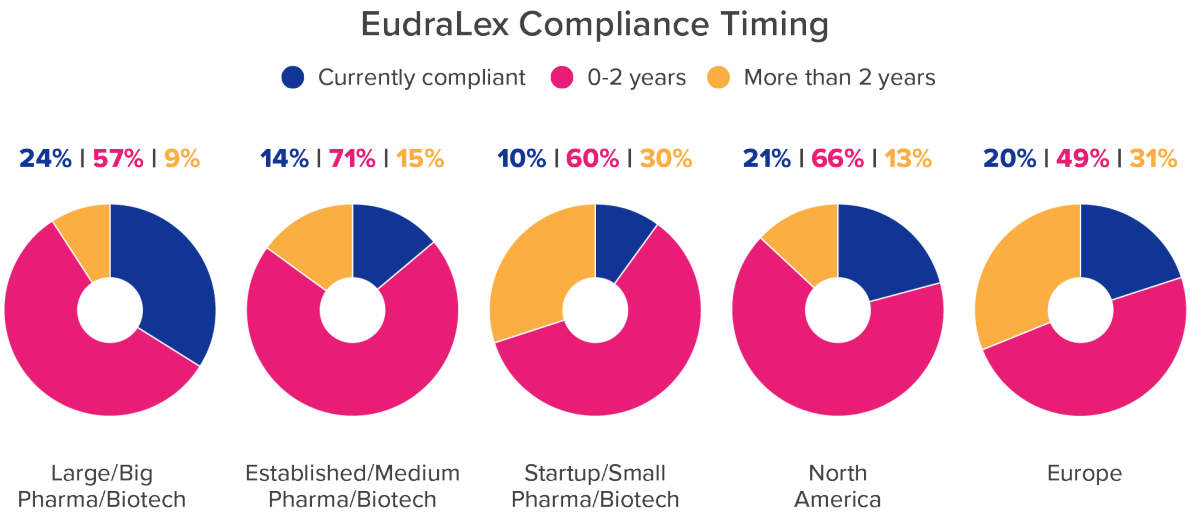
THE EUDRALEX ANNEX 1 DEADLINE IS PLAYING OUT DIFFERENTLY IN EUROPE AND THE US

After seven years of draft review, comment and revision, EudraLex Annex 1 is now in effect and companies must be compliant. It's an extensive set of regulations. This update—the first since 2008—is more than triple the length of the previous guideline. The increase isn't surprising, as there have been significant advances in drug therapies, production technology and facility design over the last 15 years.

Our survey data revealed differences between the European and North American respondents in both the predicted timeframe for meeting compliance requirements and the capital spend required.

FIGURE 7.3

What is your site's anticipated timeline to be fully compliant with the 2022 revision for EudraLex Annex 1?



Source: CRB

It may seem odd that European companies are predicting a longer path to full compliance than their North American counterparts. However, we believe that the players in the European market look at EudraLex Annex 1 through a more involved lens as they are interacting with their home country regulatory bodies on a more frequent basis. They know there is a lot of work to be done, and that translates into a longer timeframe to being compliant with Annex 1.

While the regulations have been published and the industry as a whole is working together to understand and become compliant with them, it's difficult to know how they will be interpreted until inspectors start visiting facilities.

Inevitably, there will be various interpretations made—by country and by individual inspectors. We will understand these better over the next few years, and we expect that for several years to come, companies will still be reacting to the Annex 1 revisions as regulatory interpretation becomes clearer.

In the US, however, respondents are reporting swift timeframes to compliance. We expect this is due to a primary focus on FDA requirements. As we learned in Section 2, while most North American companies are predicting a healthy growth, their plans for expansion are within existing territories. They know the regulations and nuances of the local codes and their predicted route to compliance is aligned with that knowledge.

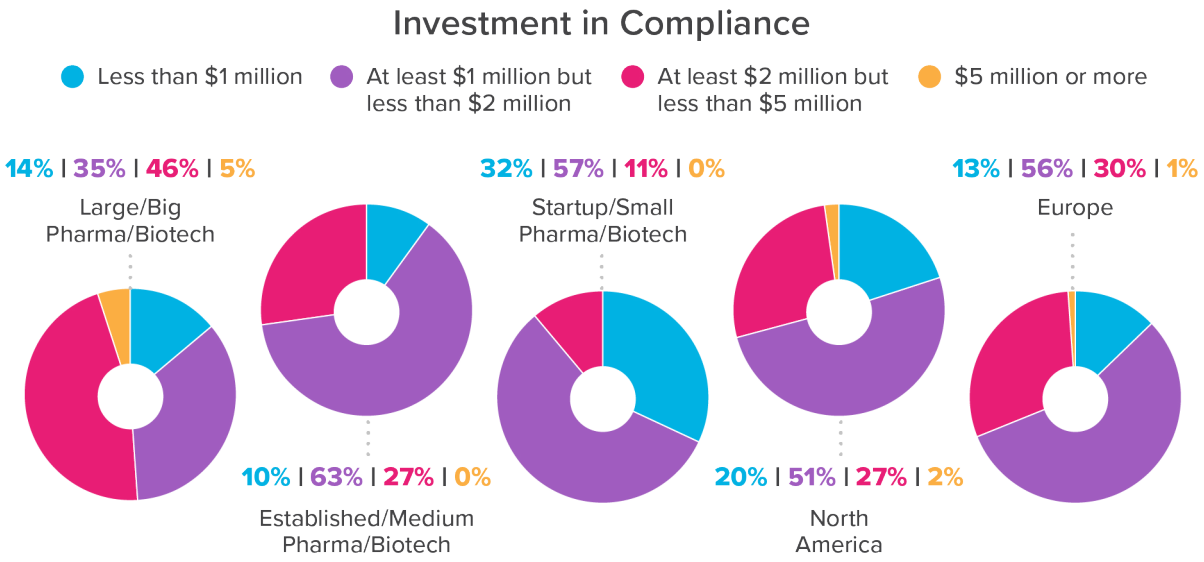
INVESTMENT IN COMPLIANCE

Our rough calculations indicate that our respondents are investing more than half a billion dollars to meet the updated Annex 1 regulations.

In Europe, there is a greater spend; our interpretation is that companies have been investing to meet the compliance requirements of Annex 1, and they anticipate a likelihood of spending more as the new regulations are put through their paces. Additionally, the clarification of background grades required for open isolators may also be driving European-based manufacturers who sell only to Europe to make significant facility modifications (upgrading room classifications and adding additional airlocks and gowning) to be compliant.

FIGURE 7.4

What is your site's expected total monetary investment (e.g., capital, legal, refiling, etc.) required to become fully compliant with the 2022 revision for EudraLex Annex 1?



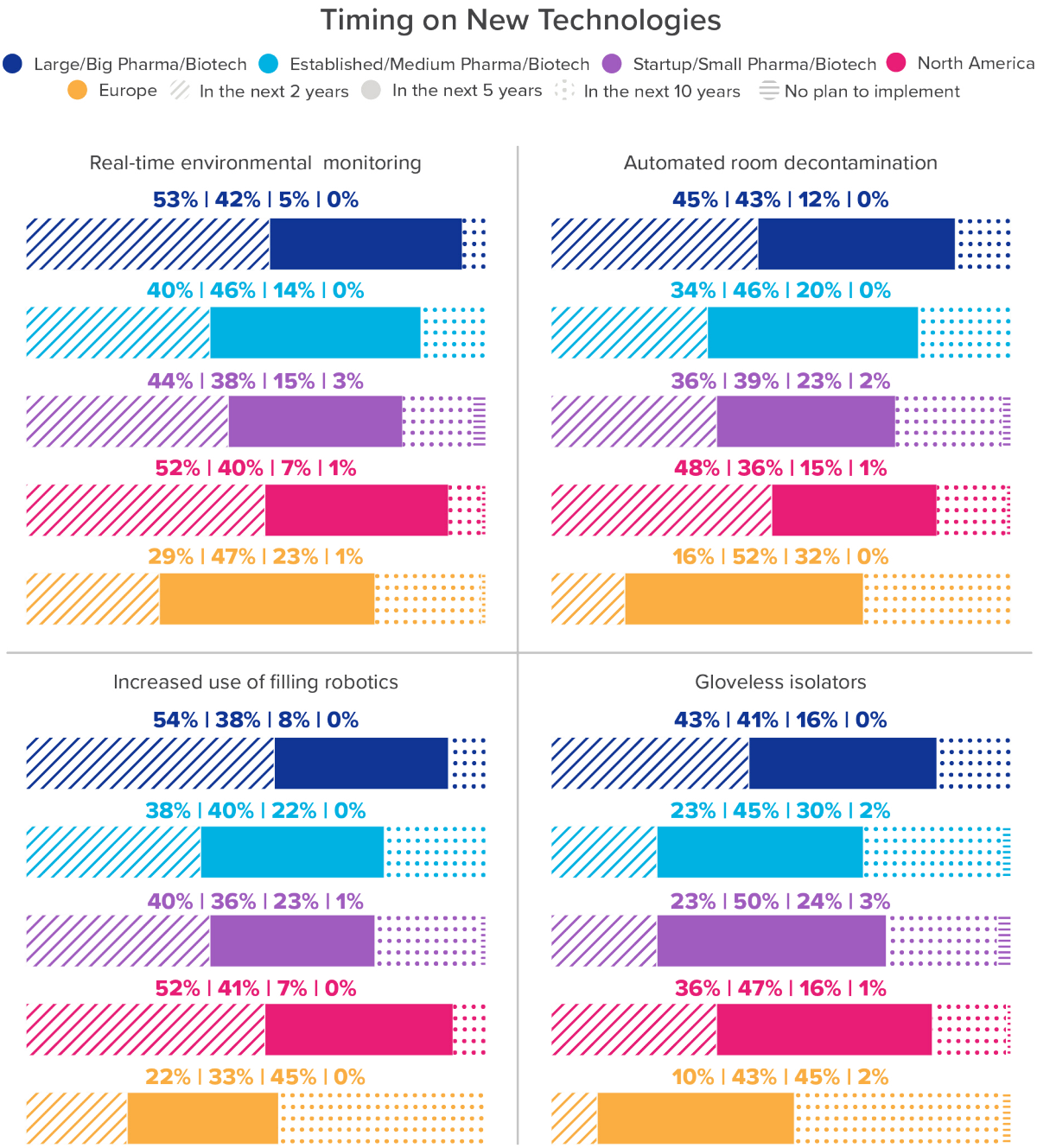
Source: CRB

This may also be the reason these European companies are looking at longer timelines for new technologies: funds are tied up in compliance initiatives.

European companies may be focused on becoming compliant with the current processes and equipment. They seem wary of investing in some of the new technologies (e.g., real-time environmental monitoring and gloveless isolators), which do not have a clear regulatory path to acceptance.

FIGURE 7.5

When, if at all, is your site planning on using the following types of new technologies?



Source: CRB

In North America, where there is less focus on Annex 1 and a lower spend on compliance, companies appear to be pushing ahead with new technologies in the shorter term.

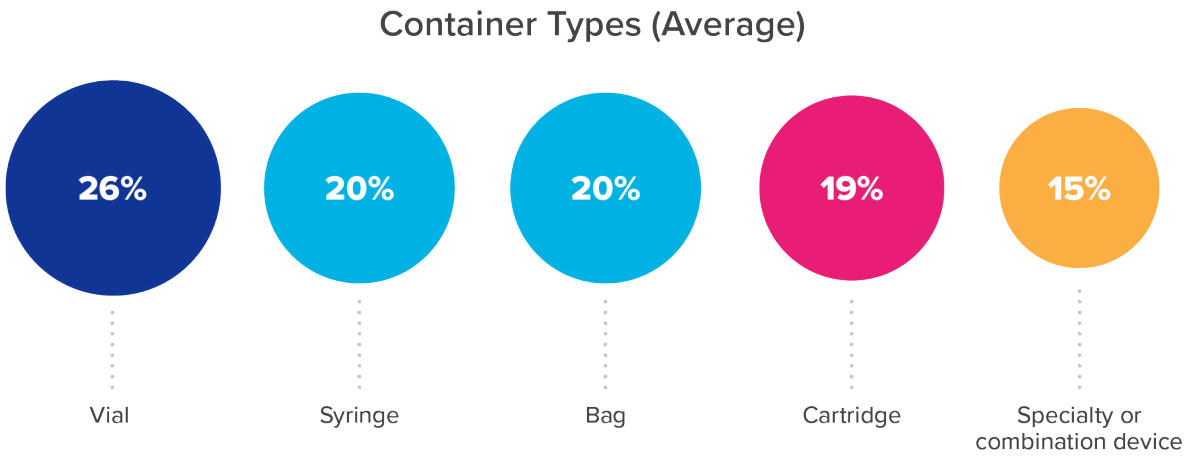
A DRIVE TOWARD INCREASINGLY SPECIALIZED EQUIPMENT AND/OR FACILITIES

The industry is getting more specialized in the way drugs are produced and packaged. Responses to the research into alternatives to cryogenic storage temperatures, new technologies, container types and batch size ranges (patient population of one for advanced therapy medicinal products (ATMP) to multi-million patient blockbusters) indicate that we are moving toward uniquely designed aseptic and sterile product facilities.

The data predicts the use of a variety of container types, with vial, syringe, bags and cartridges being almost evenly distributed among our respondents.

FIGURE 7.6

In the next five years, approximately what percent of your site's products will be using the following containers?



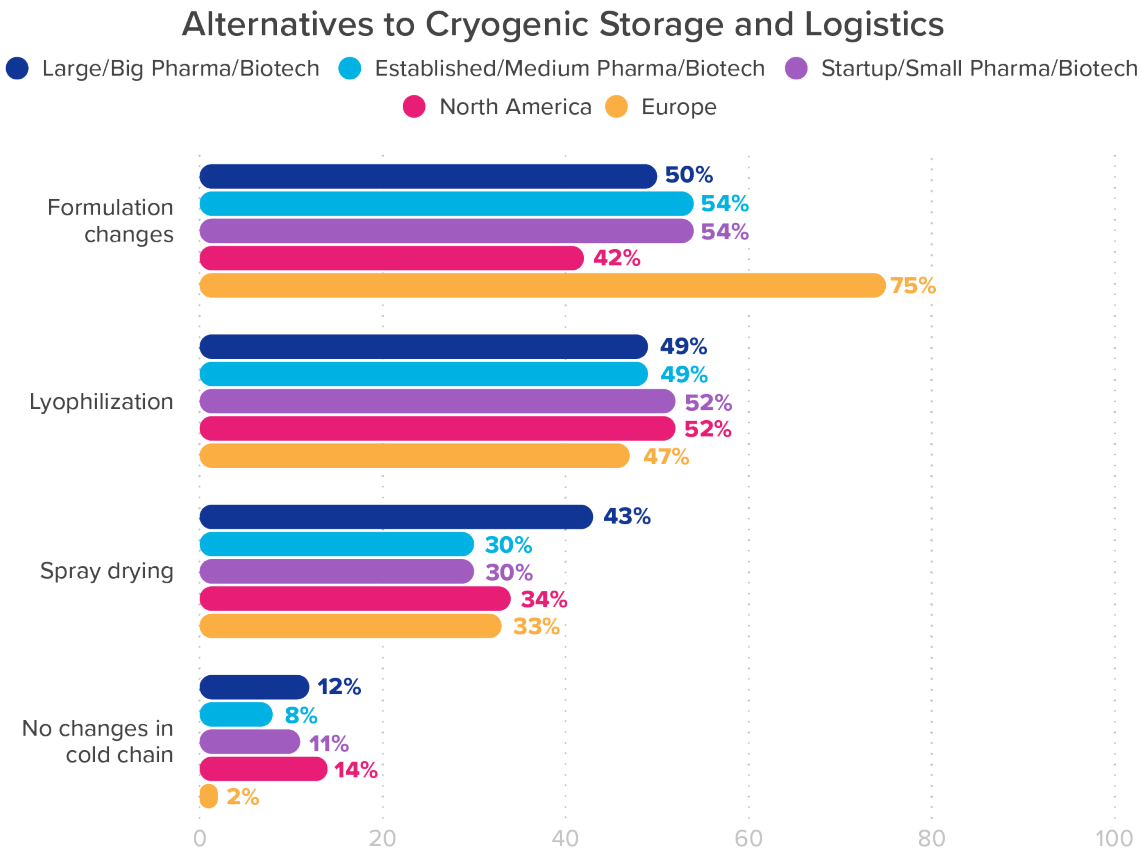
Source: CRB

As we all know, the long-established mRNA vaccine platforms were tested and put into market at record speed for COVID-19. As a result, drug stability through ultra-low temperature freezers is the norm across the board; there simply wasn't time to investigate other options.

Now, however, companies are investigating other methods for stabilizing these drugs, including formulation changes, lyophilization and spray drying. Each of these processes require specialized support systems in the aseptic and sterile product space.

FIGURE 7.7

For the products that use cold chain management, what changes is your site planning to implement in the next five years?



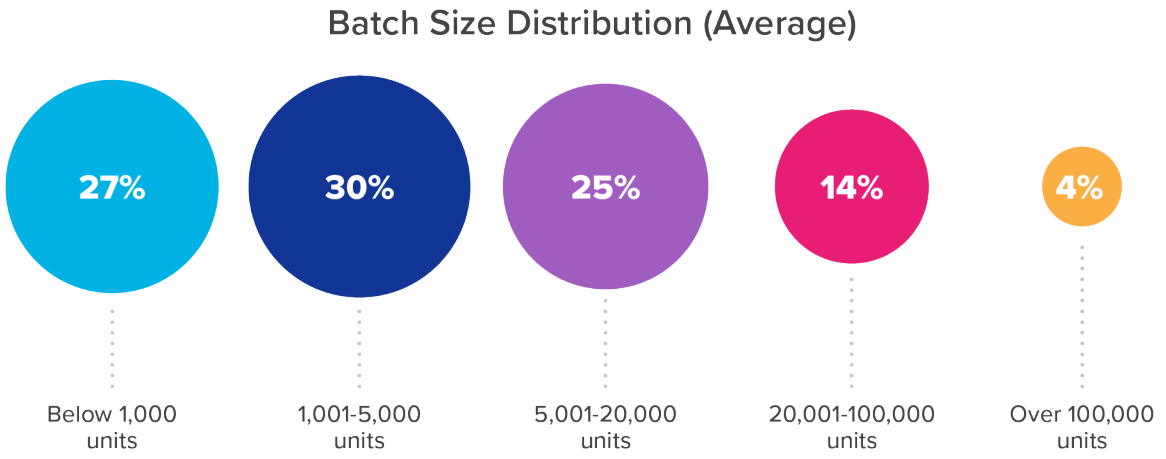
Source: CRB

Notably, European companies are researching these new technologies at a higher rate than their North American counterparts. In Europe, there is more focus and motivation to reduce energy use as energy prices are higher. And with space at a premium, techniques that don't require cold storage and transport are appealing.

Our respondents report a wide range of batch sizes, from less than 100 units up to 100,000. The numbers are split fairly even, particularly in the up to 20,000 range. Clearly, facility design changes drastically with scale, not just for equipment sizing and functionality but also for material and personnel movement. This is another argument for purpose-built facilities that can scale and meet unique product complexities.

FIGURE 7.8

What percent of your site's production is dedicated to the following ranges of batch sizes?



Source: CRB

In addition to the information gathered from our survey respondents, the filling line equipment manufacturing partners and contract development and manufacturing organizations (CDMOs) are seeing significant demand for blockbuster drug products to address diabetes, obesity, arthritis and other long-term, large patient populations. Speed to market and the need for market saturation and continued supply will drive facilities that can produce large quantities of these blockbusters quickly, efficiently and continually.

As conjugated drugs continue to enter the market, companies must consider the potential risk they pose to operators. In addition to cross-contamination concerns, thresholds for occupational exposure limits (OEL) are predicted to decrease, possibly due to increased drug potency, with 44% of respondents indicating that they will implement a 50 nanogram threshold in the next three years.

44%

will implement a 50 nanogram threshold in the next three years

To ensure patient and operator safety, the facilities built or retrofitted to fill, inspect and package these products will need higher levels of engineering controls through facility and equipment design, as well as procedural controls to ensure appropriate containment. Due to these risks, multi-product suites become harder to change over and achieve efficient active production timelines which affect throughput.

The future is not one-size-fits-all

While the EudraLex Annex 1 deadline may have passed, it will take some time to see how inspectors interpret the new guidelines. This uncertainty appears to have a greater impact on European companies than those in North America, who are focused on growth at home.

Regardless, we're seeing companies forging ahead with new products, technologies and processes. We expect that this will affect the design of facilities and equipment, with moves toward more specialized facilities, or at least areas within them, to safely and efficiently meet rapidly expanding needs in the life sciences arena.

Containers and dosing devices are also becoming more specialized and complex. The future will likely hold more patient- and clinic-friendly devices that provide higher quality and protected products, beyond vials and simple syringes. These devices will be filled on lines that reduce human intervention and the risk of contamination. And the containers will be filled with new, more complex formulations that will require special handling before filling and through inspection, secondary packaging and distribution. Materials and containers will continue to change to support the critical process parameters associated with keeping a product sterile and stable all the way to the patient.

Embracing data and AI:
Digital maturation continues despite questions about its value in manufacturing and quality

By: Niranjan Kulkarni and Ryan Thompson

Section 8

Cloud computing, machine learning, blockchain, virtual reality, advanced robotics. There's a lot of hype about transformative digital technologies, and people in many industries have high expectations. Amazon is the poster child for a data-driven organization that's been able to scale to enormous growth because it embraced these technologies. Comparatively, manufacturing lags far behind in terms of adopting data and artificial intelligence (AI), especially the life sciences. This seems poised to change.

In our *Horizons: Life Sciences 2022* report, we found most of those surveyed considered their company to be at least at Level 3 of the Digital Plant Maturity Model (DPMM), which refers to a connected facility with a high level of automation, and a strong intention to progress. We're witnessing burgeoning interest in AI—as exemplified by the embrace of ChatGPT—and enthusiasm among C-suite executives. Here we take a closer look at how life sciences companies are using data and AI.

ALMOST EVERYONE HAS A STRATEGY TO COLLECT, ANALYZE AND USE DATA

Of the 506 respondents, 93% have either already implemented or are implementing a strategy to collect, analyze and use manufacturing and quality data (Figure 8.1). This was true of companies of all sizes, though startups and smaller biopharma companies were less likely to have a strategy in place.

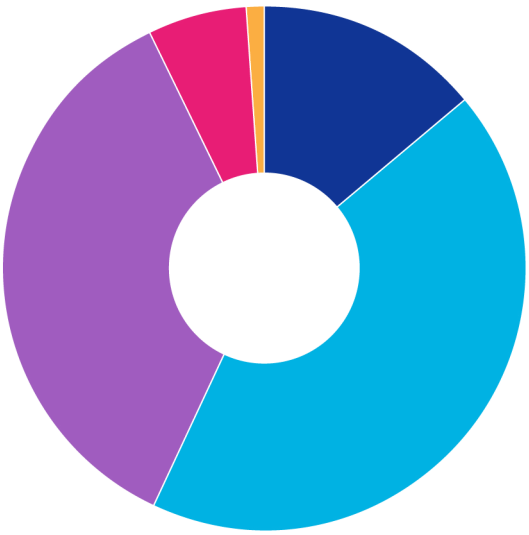
Key Takeaway:

Most companies are well on their way to implementing data strategies—and the budgets to support them—in the next two years.

When we compare responses to those of our *Horizons: Life Sciences 2022* report, this suggests companies are following through with their desire to reach the next level of digital maturity. Developing a robust data strategy is a key piece of infrastructure to reach DPMM Level 3, which unleashes the benefits of advanced analytics, AI and machine learning at scale.

FIGURE 8.1

Does your company have a strategy to use the manufacturing and quality data it's collecting?



Strategy to Analyze Manufacturing and Quality Data

14%	Yes, it is embedded in our culture
43%	Yes, it is actively in use
36%	Yes, it is currently being implemented
6%	Yes, there is a strategy, but it is not yet being enacted
1%	No

Source: CRB

Strategies are in place to use AI tools within two years

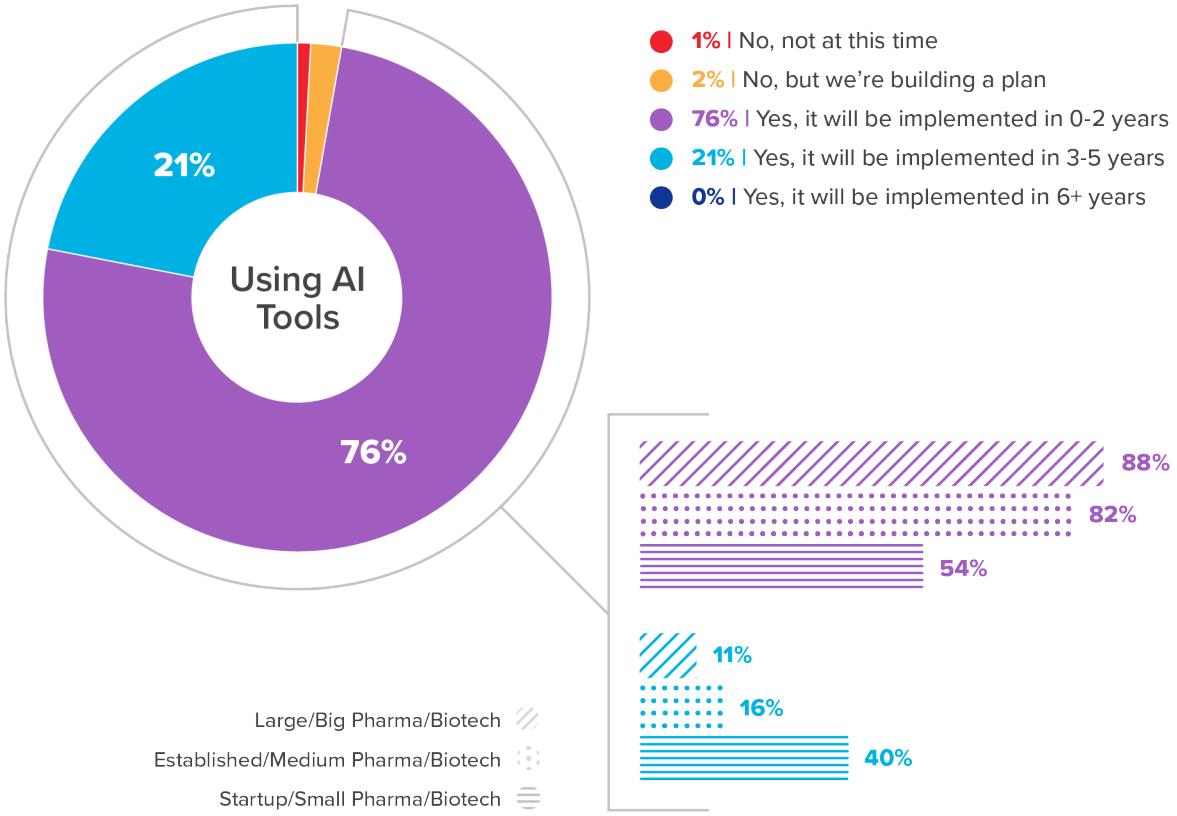
Three-quarters of respondents indicated their companies will implement a plan to use AI tools within two years (Figure 8.2), reflecting the rapid uptake of these technologies in the industry.

Startups and smaller companies were more likely to have a strategy that could take as long as five years (40%) (Figure 8.2). This could reflect a greater focus on the science of developing products than on what it means to operate in a CGMP environment. We're concerned this could be short-sighted. Adopting a mindset of manufacturing in the early stages can lead to significantly faster technology transfers and reduced time for regulatory filings. Further, with the flexibility and scalability of Cloud and software as a service (SaaS) offerings, it's often cheaper to take this

approach versus developing complicated, paper-based data collection programs and incurring the associated technical debt.

FIGURE 8.2

Does your company have a strategy to use AI tools (e.g., ChatGPT, pattern recognition, etc.)?



Source: CRB

BUDGETS ARE MOSTLY SUFFICIENT

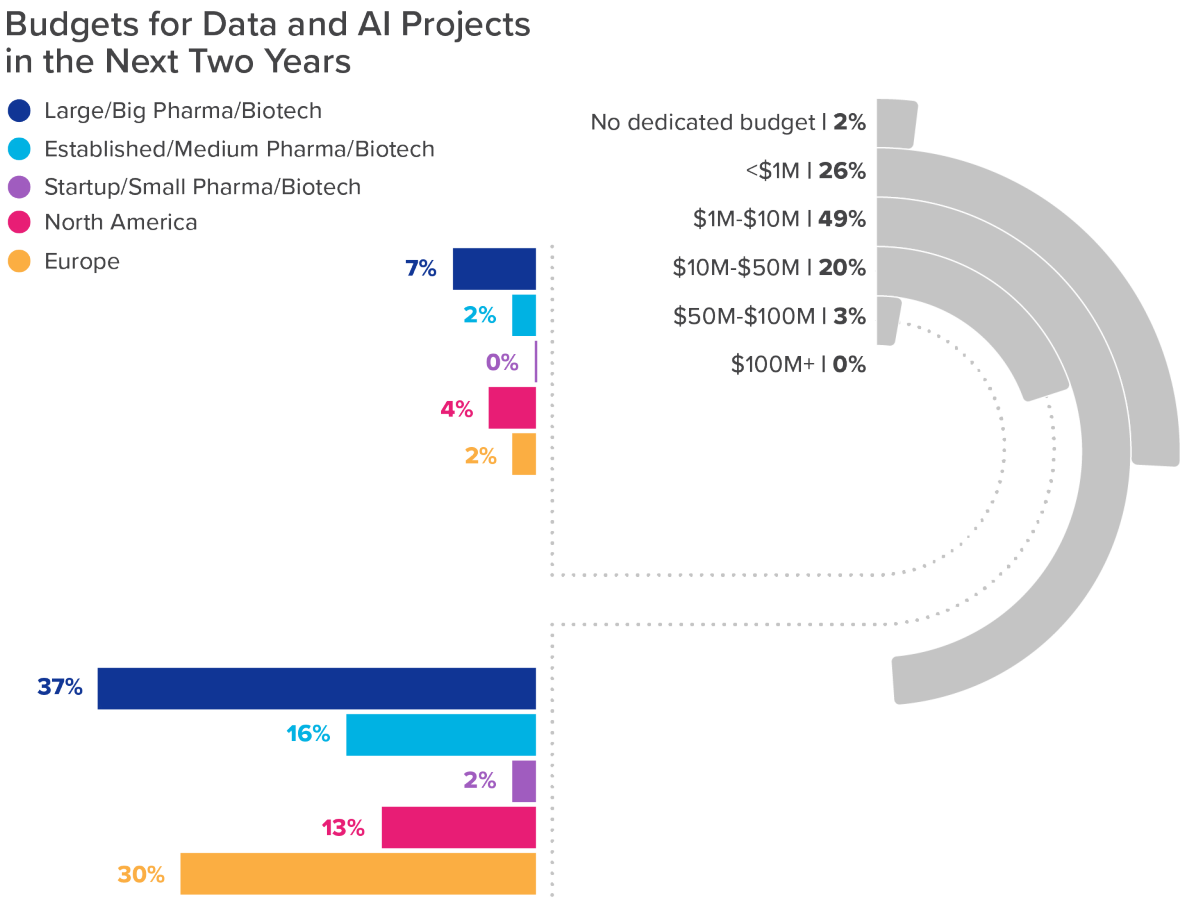
Most sites have a budget in the next two years of at least $1 million (72%), with 20% having a budget of $10–50 million (Figure 8.3). We think these budgets should be sufficient at the site level—but not necessarily for the entire network—to reach the next level of digital maturity, depending on the current state of infrastructure at any specific facility.

There were significantly more respondents from large companies whose site had a budget of at least $10million (44%) than startups and small companies (2%), and those with this budget were more likely to be in Europe (32%) than

North America (17%) (Figure 8.3). Since Industry 4.0 and Pharma 4.0™ initiatives began in Europe, this finding may suggest that the life science community there had a head start. This is likely also related to Europe-based facilities being more inclined to believe in the benefits, as we discuss in more detail below (Figure 8.6).

FIGURE 8.3

What's your site's overall budget for data and artificial intelligence projects in the next two years?



Source: CRB

R&D AND QUALITY ARE OFF TO A HEAD START—MANUFACTURING WILL FOLLOW

Respondents pointed to drug discovery and quality/regulatory concerns as the two areas receiving the greatest investment with respect to digitalization (Figure 8.4).

1. Drug discovery and R&D

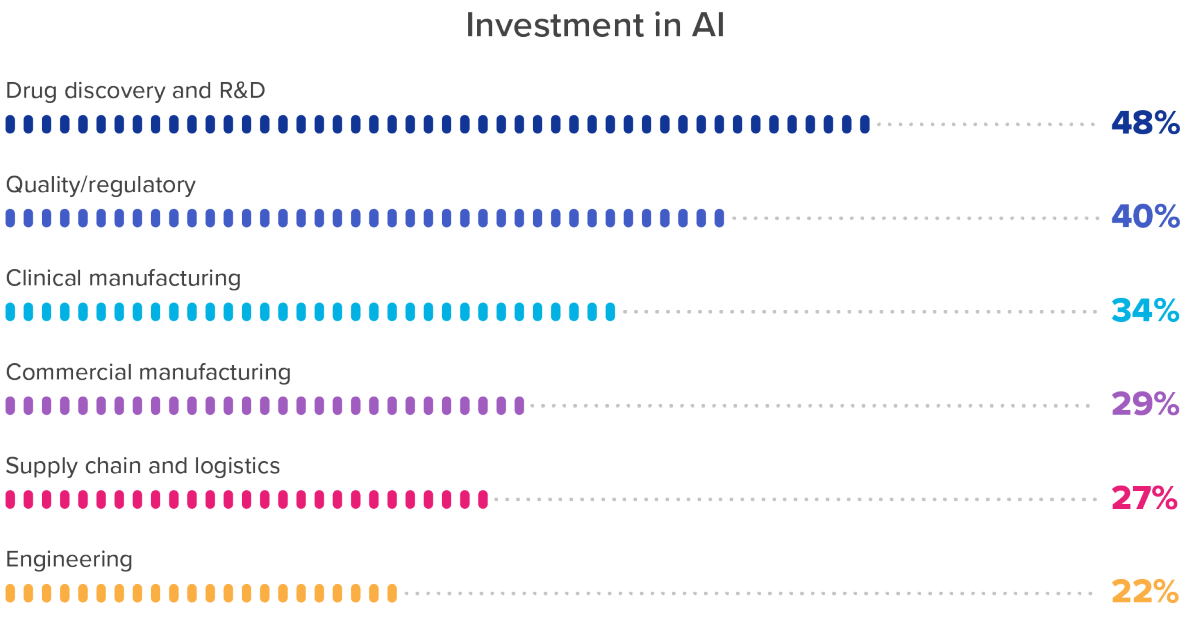
That almost half of respondents said their companies were devoting the most capital to R&D is in keeping with our client experience. Many use AI to design molecules, for example, which is less complicated from a regulatory standpoint because of the lower safety risks involved and the lack of change controls and validation. Combined with the potential for enormous benefits of discovering a revolutionary new therapy, this lines up to a low-risk, high-reward scenario. Manufacturers seem to agree and may be moving resources from CGMP manufacturing to digital tools—especially AI—in R&D, as discussed in Section 2 of this report, "Planted, not buried: The life science industry prepares for new growth."

2. Quality and regulatory

The cost of quality control and regulatory compliance for life sciences companies can be significant, which is confirmed by the 40% who indicated that this area is receiving the most investment at their companies. There are many compelling use cases for data and AI to serve quality and regulatory needs, including using compliance with data integrity ALCOA+ principles, release by exception and quality by design (QbD) initiatives.

FIGURE 8.4

What two areas of your company are receiving the most investment with respect to data and artificial intelligence?



Source: CRB

Key Takeaway:

Drug discovery receives the bulk of funding for data and AI, followed by quality/ regulatory areas; manufacturing—both clinical and commercial—is an area poised for growth.

Expect the use of data in manufacturing to grow

While fewer of those involved in the industry chose clinical and commercial manufacturing, our experience tells us the use of data collection and analysis in manufacturing will grow. During manufacturing, data analytics can help:

- Speed up technology transfers occurring between clinical and commercial manufacturing
- Improve production efficiency and reduce labor intensity, which is a challenge for all manufacturing, not just life sciences
- Optimize biologics processes
- Include signature timestamps from each batch record to pinpoint where manual operations throttle a process

Moving raw materials and finished goods will benefit from digitalization

While only 27% of respondents said their company was prioritizing funding for digitalization in supply chains, there are substantial gains to be made by doing so. Uber Freight is a prime example of how to use data to facilitate the movement of goods and people. It promotes transparency and streamlines operations, develops a hybrid transportation network—relying on drivers and autonomous trucks— and creates a better experience for drivers by collecting, analyzing and applying data.

THE C-SUITE HAS TAKEN RESPONSIBILITY FOR INDUSTRY 4.0

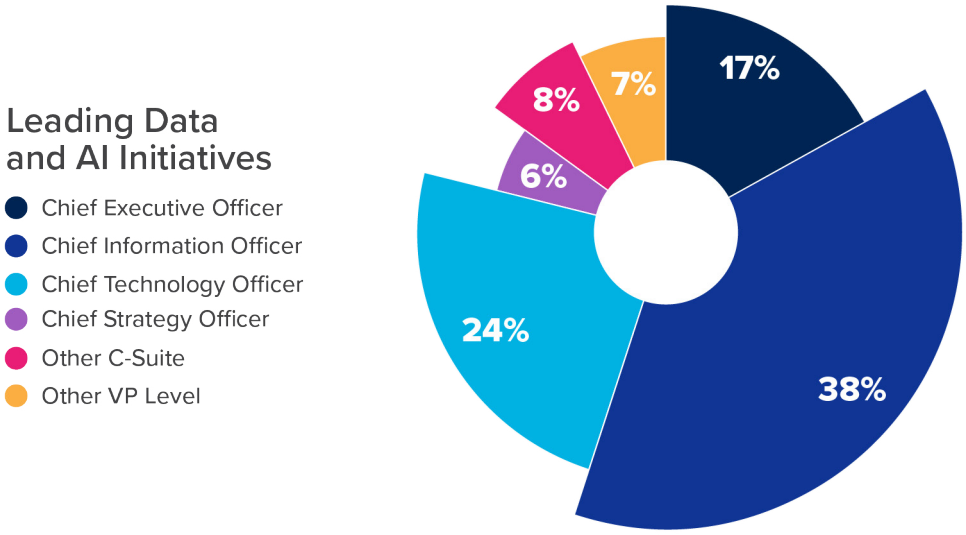
The leaders of Industry 4.0 are overwhelmingly in the C-suite of most companies (Figure 8.5). It's great to see this level of ownership, which makes it more likely that these transformations will happen.

Key Takeaway:

Digital transformations are led by the C-suite, ensuring this is a strategic goal involving processes and people, not just a technology project.

FIGURE 8.5

Who is responsible for leading your company's data and artificial intelligence initiatives?



Source: CRB

WHAT'S HOLDING AI PROJECTS BACK?

When respondents were asked about the challenges preventing their companies from adopting data and AI projects, the top issues were either technological, a lack of market clarity or regulatory concerns (Figure 8.6).

Many don't believe the hype, especially in the US

While budgets may be sufficient, real and perceived barriers might be preventing more companies from embracing data and AI. A large number cited lack of evidence of a return on investment (ROI) for Industry 4.0 initiatives (43%), and this was substantially higher for North American companies (48%) than their European colleagues (28%) (Figure 8.6). Additionally, 28% pointed to market confusion as a significant barrier. Why is this?

Key Takeaway:

There remains cynicism that investments in digitalization will yield dividends.

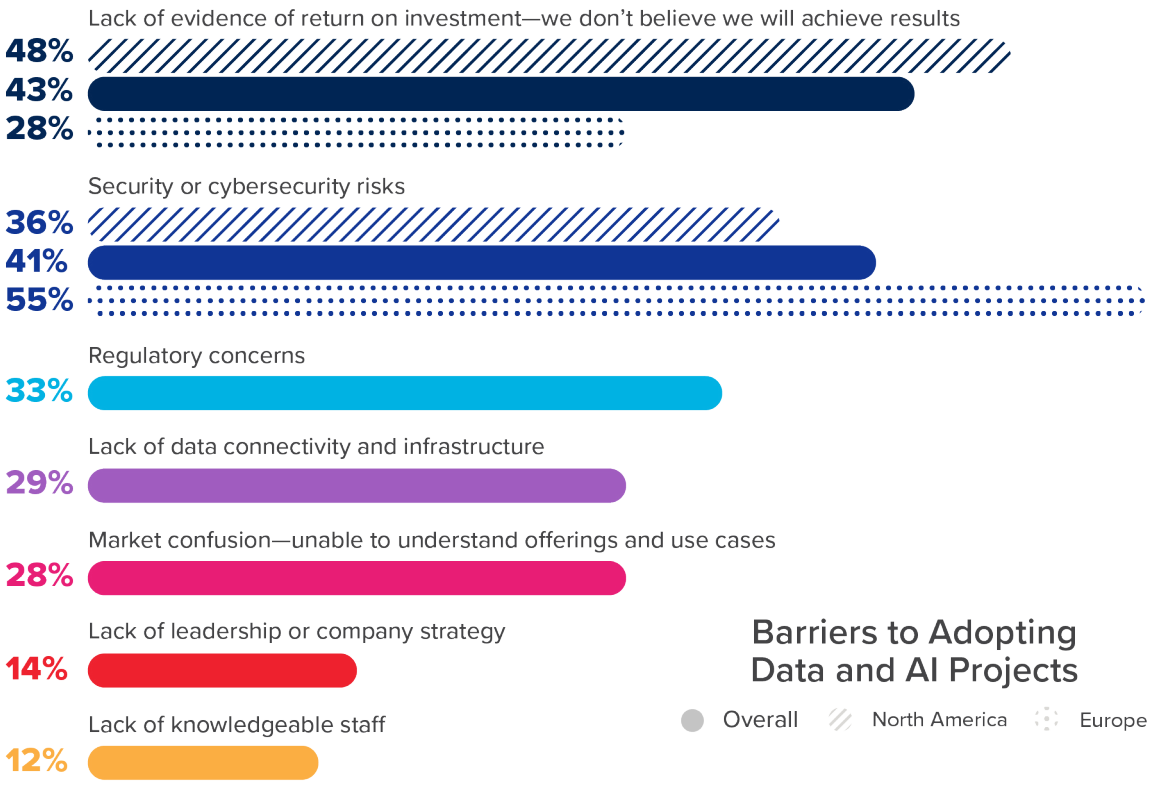
It's impossible to measure ROI for a digital transformation using the results from a single project—the value will be obscured by high infrastructure costs, as well as the inertia of changes to roles and business processes. Instead, companies should rely on a longer time horizon (three to five years) to assess the potential benefits, as well as measuring a variety of KPIs.

To us, this points to a lack of understanding among a subset of respondents about how to apply digital technologies and, once applied, whether there's value in that digital strategy. Life sciences manufacturing lags behind other industries that use data to optimize operations, like retail and banking, because of the regulatory scrutiny of operations and the premium paid to monitor and document processes. This obscures how to achieve an ROI using data solutions in a CGMP environment, making it hard for someone requesting capital to point back to the strategic goal without an obvious direct return.

It turns out to be incredibly costly for organizations not to invest in data and AI. These tools spark creativity and new strategies to go to market and enable novel business cases. Further, it creates a culture of ownership and accountability, empowering everyone in the organization to excel. Investing in digital infrastructure could also allow a company to do things it currently can't, unleashing additional value well into the future.

FIGURE 8.6

What are the barriers stopping your company from implementing data and AI projects?



Source: CRB

Security risks were a concern, especially for those in Europe

Cybersecurity is essential—think of it as table stakes—for implementing data and AI projects, as reflected in the level of concern expressed about security and cybersecurity risks (41% overall). These concerns were even more prevalent among European respondents (55%) than those in North America (36%) (Figure 8.6). While this may reflect the stricter internet privacy laws in Europe, regulations protecting both manufacturing information and patient privacy are similar between the two regions.

Respondents' cybersecurity concerns could also be due to added costs to data projects. For instance, many pieces of equipment to collect data use older, unsecured technology platforms, making it difficult and costly to incorporate them into a corporate network. Additionally, not having appropriate information technology (IT) policies in place for patching can lead to problems and conflict when adding operational technology (OT) assets to IT networks in what is commonly known as IT/OT convergence.

Lack of skilled staff and internal leadership are not significant barriers

Only small percentages of respondents indicated that a lack of leadership or strategy (14%) or skilled workers (12%) were challenging for the implementation of data and AI projects. This is a significant difference from the *Horizons: Life Sciences 2022* report that looked at Pharma 4.0™ initiatives as a whole. As noted above, it appears the C-suite of most companies has taken ownership and is providing the necessary leadership for digital initiatives. And the supply of knowledgeable staff has grown because many universities now offer data-related courses, while other workers have gained experience in data from other industries.

COMPANIES ARE SERIOUS ABOUT DIGITAL MATURATION

Most respondents said their companies used the same amount of data and technology as—or more than—their peers. (89%). While it's impossible for the majority to be above average, when combined with adequate budgets this data reinforces our perception that people are taking digitalization seriously.

89%

of respondents said they used the same amount of data and technology as—or more than—their peers

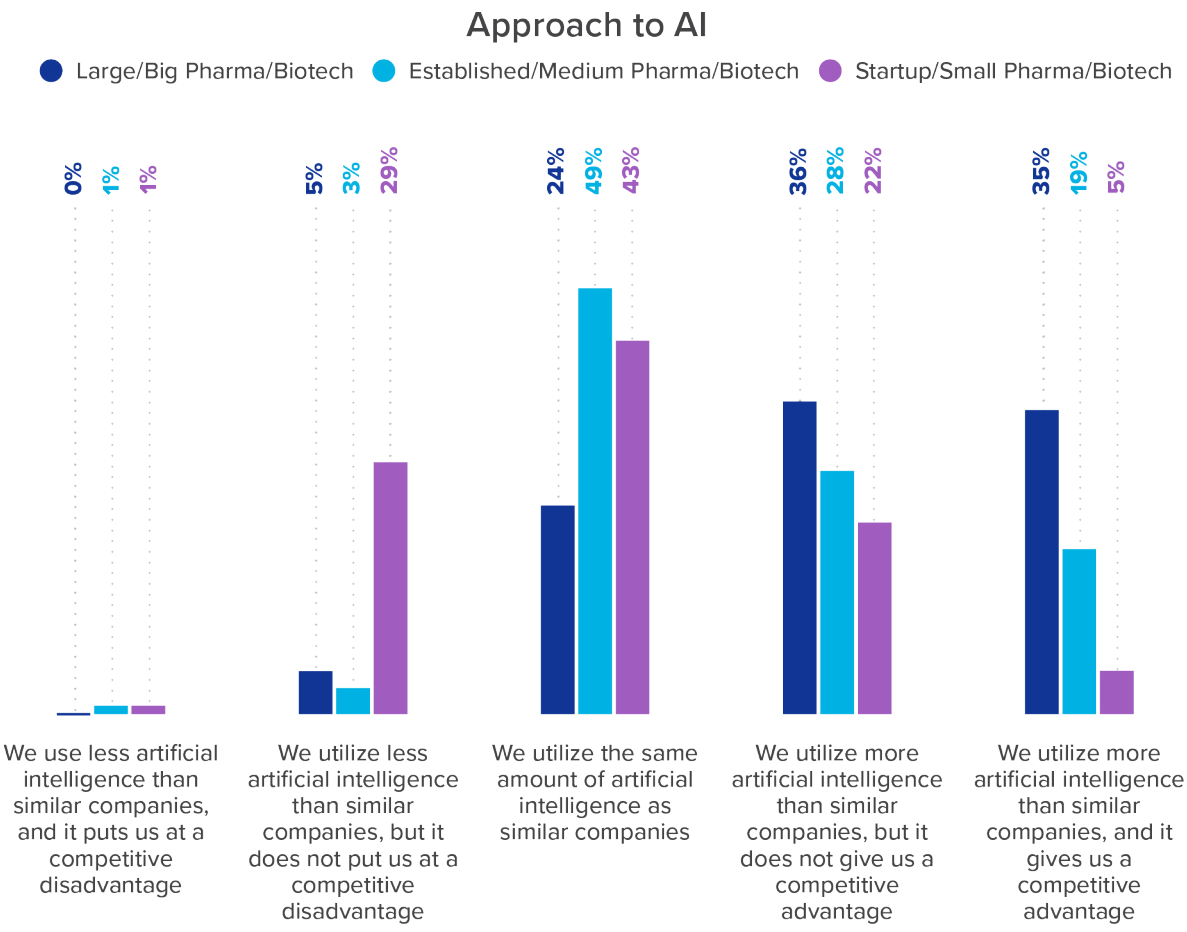
Unsurprisingly, it was the larger companies that were more likely to use AI when compared to medium and small companies (Figure 8.7). This is in keeping with the much larger site budgets earmarked for the next two years at larger companies (Figure 8.3), suggesting they're willing to invest in technologies they believe will provide them with a competitive advantage.

But, once again, they're uncertain about the value

Respondents who said their companies use more AI than their peers were split between those who think the technology provides a competitive advantage and those who did not. This confirms the data above, which indicated that the lack of evidence of ROI was the most significant barrier to adoption (Figure 8.6).

FIGURE 8.7

Where do you believe your company's approach to data and AI is with respect to your peers?



Source: CRB

Digitalization in the life sciences is catching up

The workforce is available, strategies are in place, budgets are sufficient and executives are supportive. Despite some skepticism that spending on data and AI will bolster their bottom lines, companies know there's no turning back, and they intend to push forward with digital technologies. While manufacturers may have lagged behind retail, banking and transportation in harnessing the power of data and AI, this survey of industry experts suggests we're witnessing the maturation of Pharma 4.0™.

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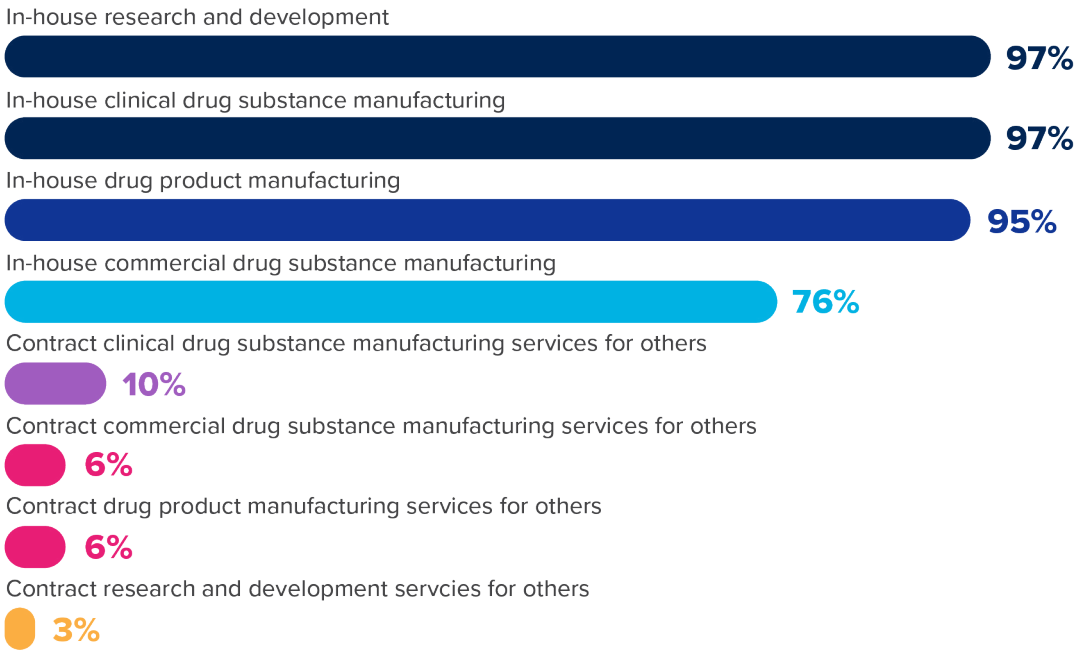
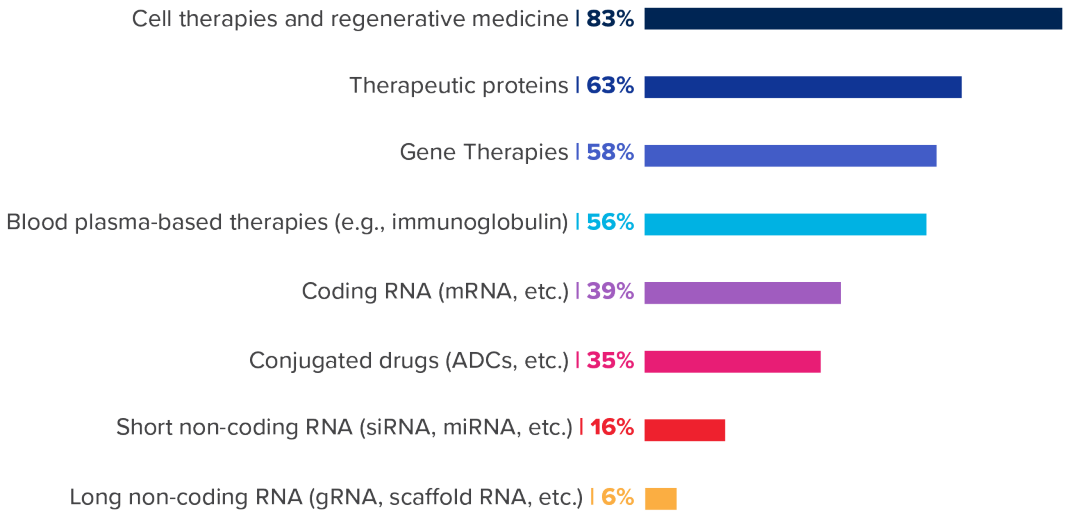
FIRMOGRAPHICS

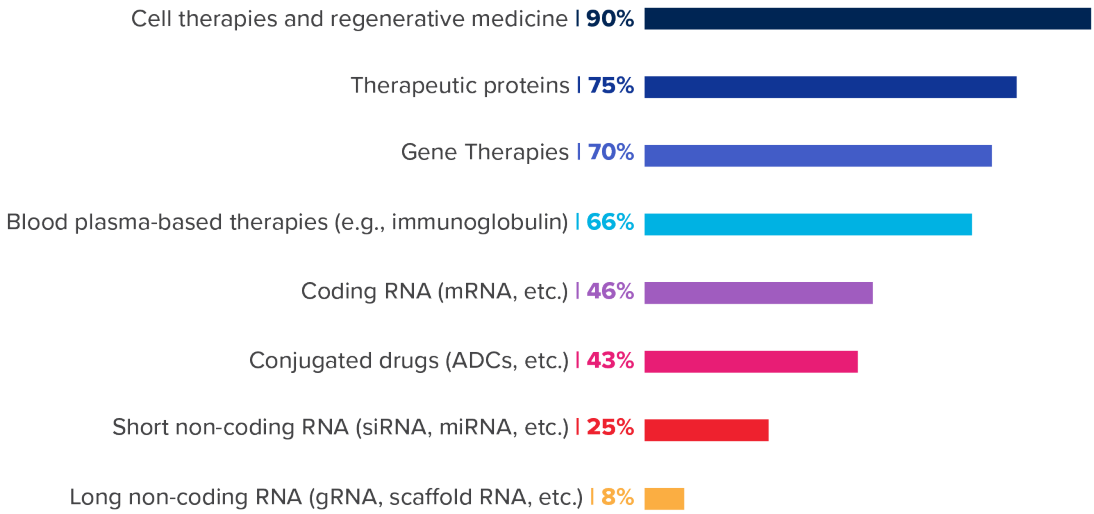
Company's Products and Services
n=506



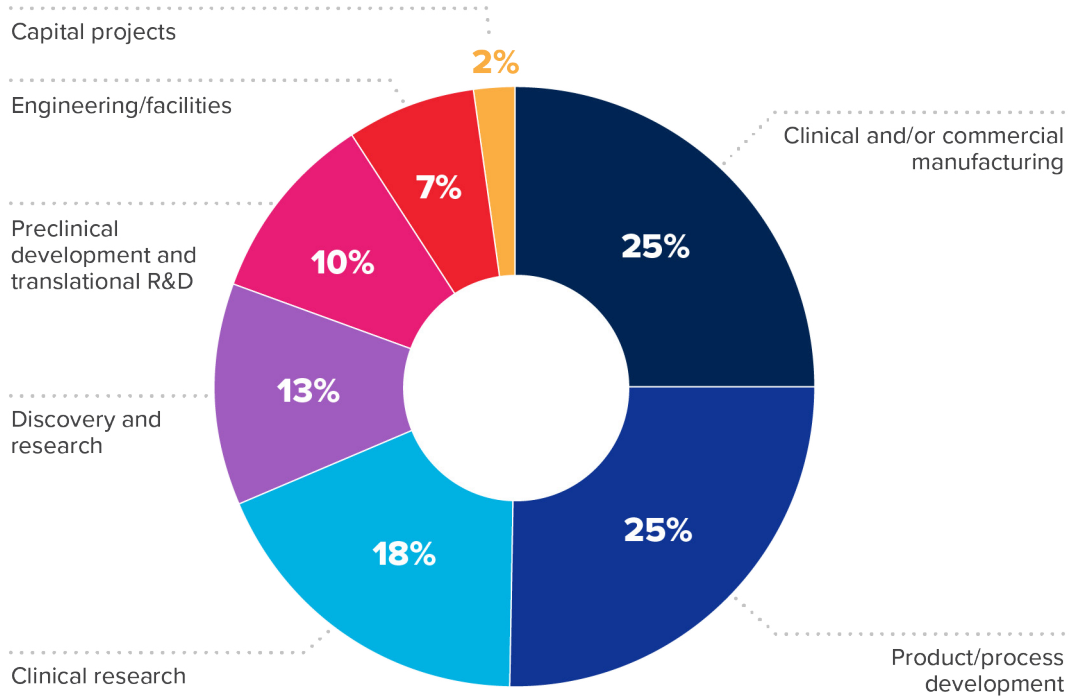
Company's Product Types



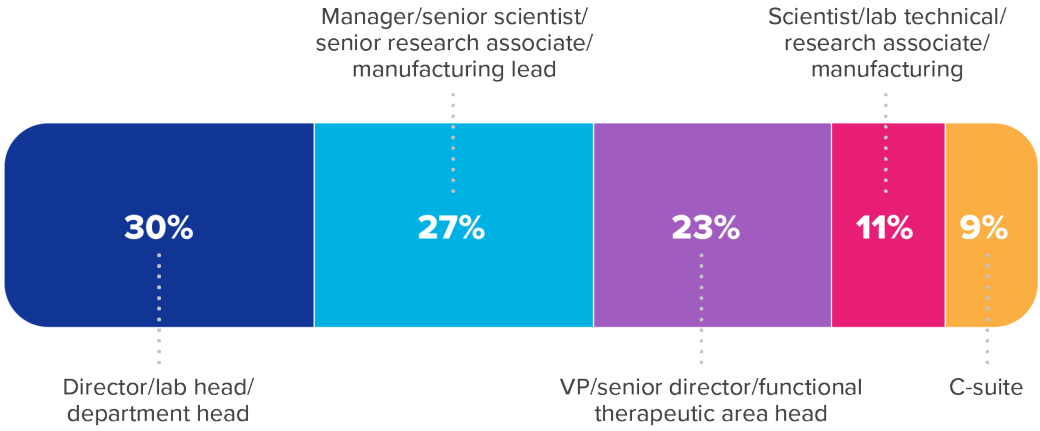
Therapy Types in Product Pipeline
(Next 3 Years)



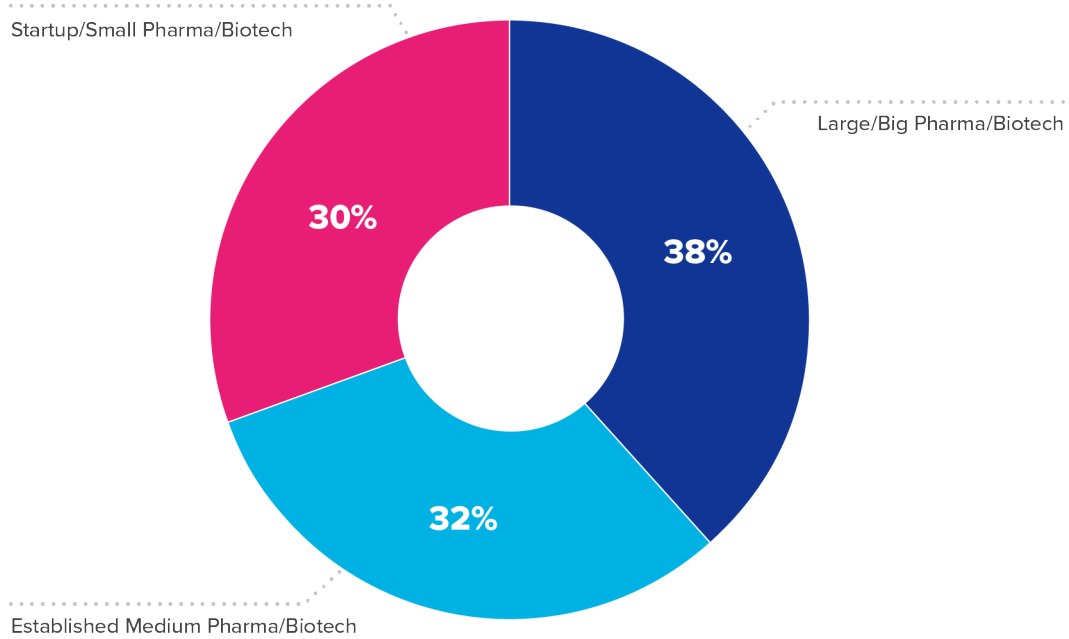
Respondent Primary Job Function



Respondent Primary Role

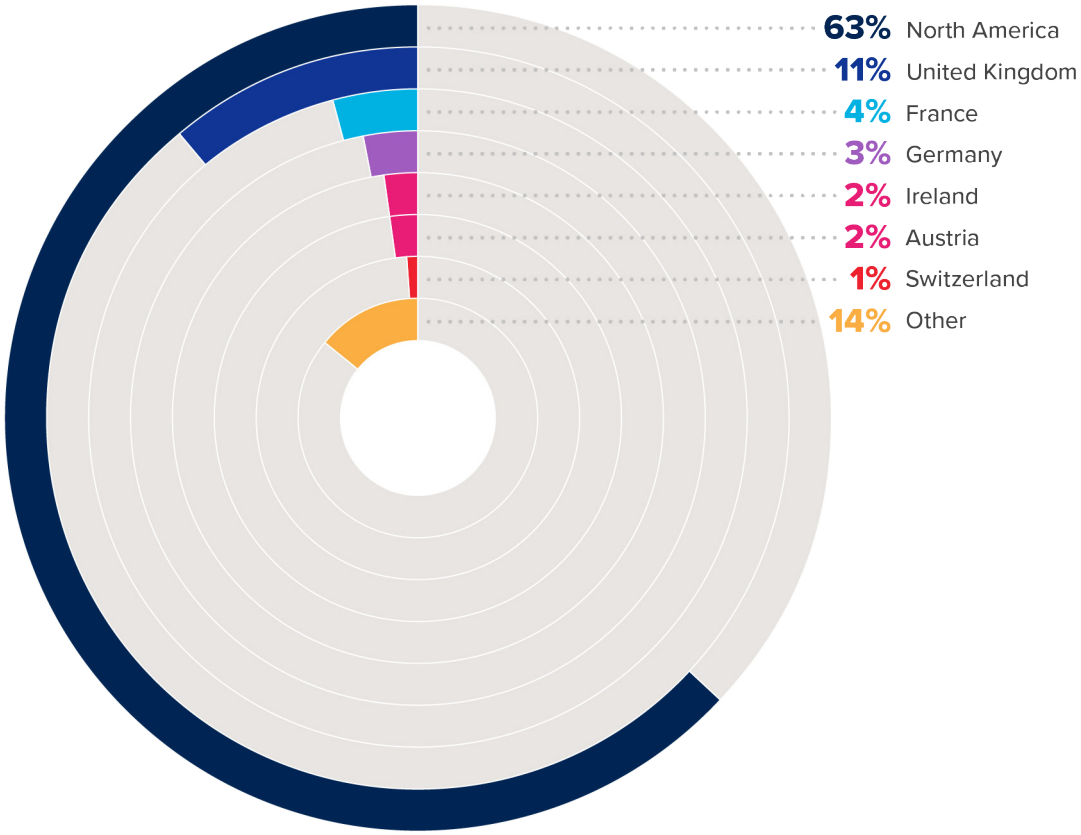


Company Size

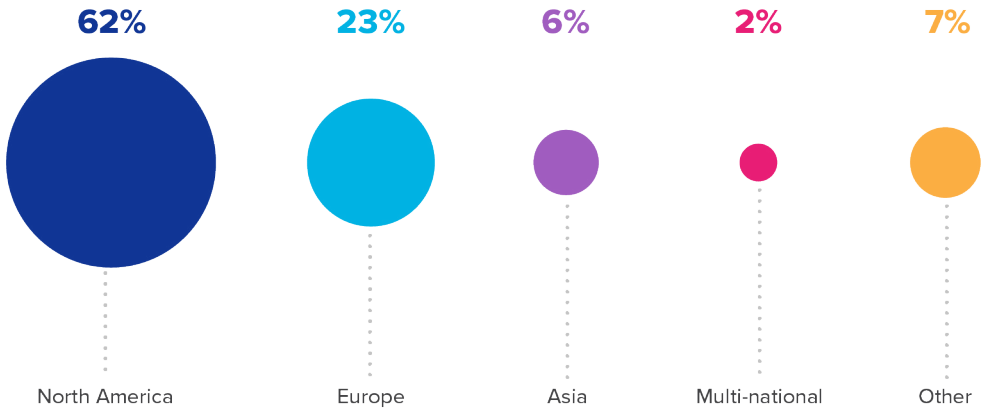


Company's Target Market for Product Pipeline

Region of Majority of Working Time



Primary Business Operations



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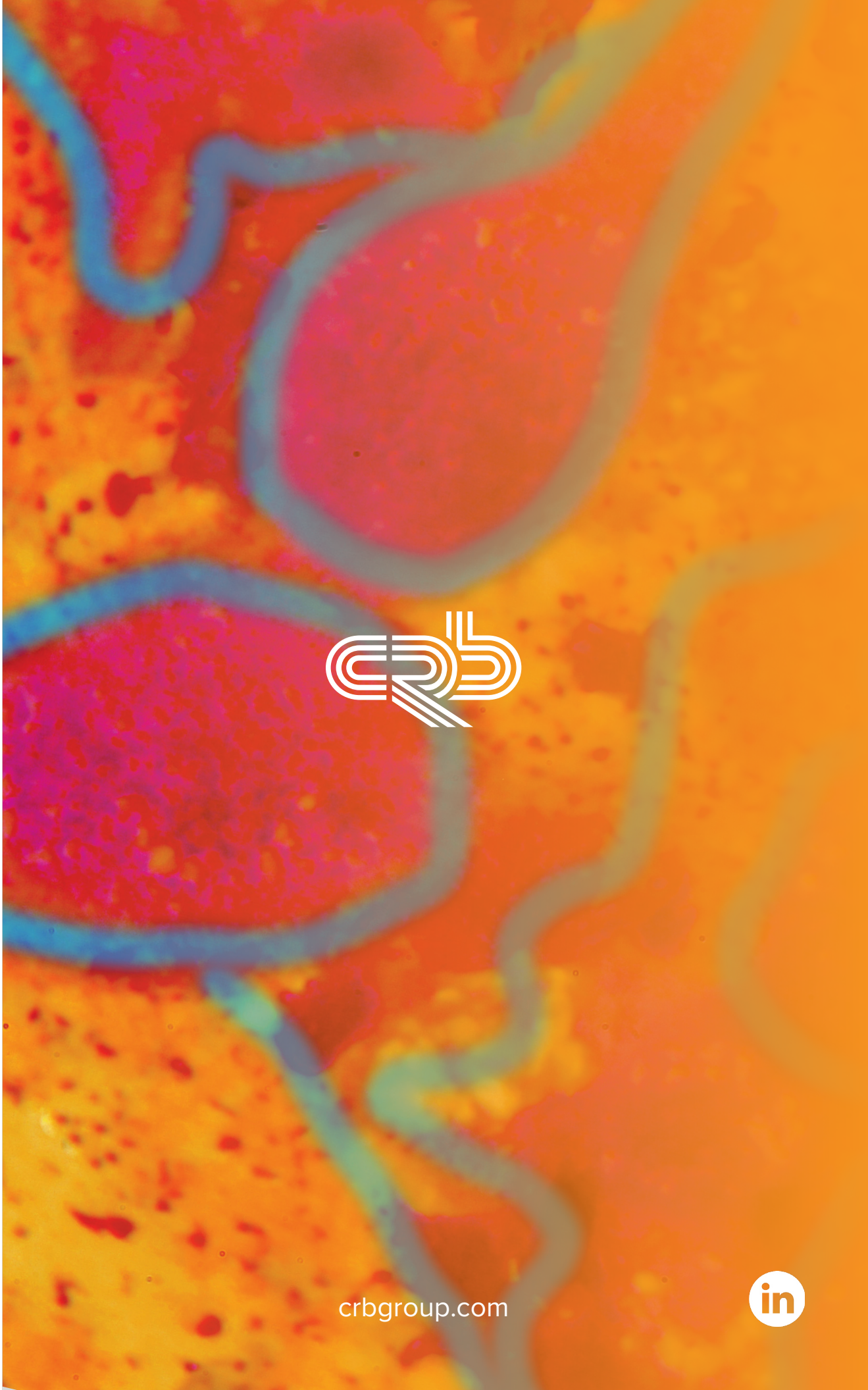

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