A TOOLKIT FOR EMERGING BIOTECHS

Practical Advice For Navigating Challenges & Advancing Clinical Development

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MODERN BIOTECHNOLOGY: AN ERA OF INNOVATION

Biotechnology is a key driver of innovation in the life sciences industry. With advances in immuno-oncology, gene and cell therapies, and microbiome therapeutics as examples, the global biotech industry was valued at $794B in 2021, and is further estimated to reach a market value of $1,684B by 2030[1]. Globally, there are more than 10,000 biotech businesses employing close to a million people[2].

The ongoing success of the biotech industry is not only revealed by its market value, but also by numerous achievements in recent years. Over the past five years, the FDA has approved an average of 51 drugs per year, up from 24 drugs per year a decade ago. In 2021, 50 new drugs were approved, most of which were designed for the therapeutic areas of oncology, neurology, infectious diseases, and cardiovascular diseases[3]. That same year saw the approval of the 100th antibody as well as the first KRAS- and HIF-2α-targeted therapeutics for cancer.

The highlight of 2021 was the landmark approval of the first mRNA vaccines. The Pfizer-BioNTech COVID-19 vaccine Comirnaty™ gained full approval in August 2021, just 1.5 years after the program was initiated. This set a new precedent, as vaccine discovery and development usually takes 10.7 years on average[3]. Comirnaty sales raked in $36.9B, making it the top-selling drug of 2021[4].

Several Nobel Prizes have also been awarded for discoveries that have proven indispensable for the biotech industry. In 2018, James Allison and Tasuku Honjo were awarded the Nobel Prize for Physiology and Medicine for their discovery of checkpoint inhibitors, which has led to the development and approval of cancer drugs that release the checkpoint brakes on the immune system[5]. Half of the 2018 Nobel Prize for Physics went to Arthur Ashkin for designing a laser that can be used to precisely manipulate molecules in cells, while one part of the Nobel Prize for Chemistry was awarded to George Smith and Gregory Winter for developing the phage display technique for the creation of novel antibodies[5]. More notably in 2020, Emmanuelle Charpentier and Jennifer A. Doudna were awarded the Nobel Prize in Chemistry for their breakthrough research on CRISPR-Cas9 as a gene-editing tool[6].

Biotech and innovation are closely linked. Since the 1950s, modern biotechnology has brought us monoclonal antibodies, novel vaccines, immunotherapies, and more. Found at the forefront of the biotech industry are large biotech and pharma companies such as Celgene, Gilead, Amgen, Pfizer, Roche, and Novartis[7]. Behind the scenes, however, are thousands of emerging biotech companies driving innovation and success.

$794 Billion
Global Industry valued in 2021

~$1,684 Billion
Global Industry projected value in 2030

10,000+
Biotech businesses

~51 Drugs
Per year have been approved by the FDA over 5 years

50 New Drugs
Were approved in 2021

EMERGING BIOTECHS: THE TRAILBLAZERS OF DRUG DEVELOPMENT

Throughout the history of modern biotechnology, emerging biotechs have left their mark and supported large pharma companies along the way. Genentech, for instance, started small, but now employs 14,000 people. In the late 1970s the company only had 12 employees. At the time, only six years after being founded, Genentech supported Eli Lilly in the development of synthetic "human" insulin; this was the first-ever genetically engineered human therapeutic and was approved in 1982[8].

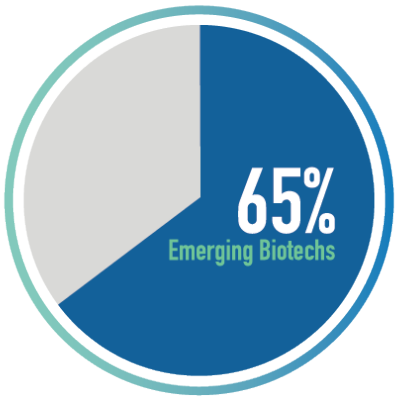
Another example in which an emerging biotech company supported pharma can be found in the success story of Humira® (adalimumab). In the 1990s, Greg Winter's Cambridge Antibody Technologies (CAT), with approximately six employees at the time, teamed up with BASF Bioresearch Corporation to develop the first fully human monoclonal antibody[9]. Adalimumab was approved by the FDA in 2002 for the treatment of rheumatoid arthritis. Today, it is one of the best-selling drugs worldwide, registering sales of $20.7B in 2021[4], coming in second behind the COVID-19 vaccine Comirnaty. Consequently, CAT and its breakthrough discovery became one of the UK's greatest biotech success stories[9].

Defined as companies spending less than $200M annually on R&D and with less than $500M in revenues, emerging biotechs continue to thrive. They are currently responsible for 65% of molecules in the R&D pipeline, up from one third in 2001, and have patented half of the new active substances approved by the FDA in 2021[10].

Emerging biotechs work at the forefront of science, often venturing into the unknown where there is little or no real-world data to work with or regulatory frameworks to work within. Though this harbors a high risk, if successful, it comes with a high payoff both in terms of patient benefits and financial gain.

For instance, more and more companies are focusing on orphan drug development: in 2019, 31% of medicines in the pipeline were targeting rare diseases, up from 18% in 2010[11]. There are more than 700 medicines in development in the US to address the unmet needs of 30 million Americans suffering from rare diseases[11], and of the 50 FDA-approved new active substances in 2021, 52% carried orphan drug designation[3].

R&D Pipeline Molecules



Emerging biotechs continue to thrive as they are currently responsible for 65% of molecules in the R&D pipeline[10].

However, developing orphan drugs is associated with many challenges, including complex science, small patient populations, difficulties collecting relevant data, and complicated logistics[12]. Despite this, emerging biotechs have been frontrunners in the orphan drug space, and only recently has large pharma entered the rare disease market. In fact, the term "orphaning" was coined to reflect the disinterest of large pharma, as developing these drugs was not seen as lucrative[13].

This increase in activity in the orphan drug space is mainly due to the efforts regulatory bodies in the US and EU have put in place to make this area of drug development more attractive: providing fast track programs, market exclusivity, reduced regulatory fees, tax reductions, and other benefits for those companies working on orphan drugs[12].

But it is not only orphan diseases that have received more attention from emerging biotechs. As of March 2021, more than 95% of the anti-infection/antimicrobial drugs in the pipeline were being developed by emerging biotechs, with 70% of the companies considered pre-revenue. This follows on the heels of large pharma mostly exiting the market and the launch of the AMR Action Fund in 2020 that aims to invest $1B in startups pursuing new antibiotics[14].

Although large pharma companies remain important partners for emerging biotechs, often co-launching drug candidates in an attempt to mitigate risks, more and more emerging biotechs are partnering with each other: in 2021, 62% of deals were partnerships between emerging biotechs; the remaining 38% involved large/mid companies, which is down from 51% in 2016[15].

Together, these numbers show that emerging biotechs are slowly taking control of their drug development processes and assets, rather than relying on big pharma companies[4]. Large pharma companies seem to be becoming less influential in originating molecules, as emerging biotechs are increasingly taking their candidates from discovery, through development, all the way to commercialization alone[4].

In this competitive industry, emerging biotechs are confronted with various challenges, especially in the early stages of compound development. This white paper will discuss the challenges biotechs face and solutions to successfully emerge from the competition with a drug candidate.

CHALLENGES FOR EMERGING BIOTECHS: WHAT'S KEEPING YOU UP AT NIGHT?

The biotech industry is a complex and challenging environment in which many small and emerging biotech companies struggle to gain a foothold. It is a fate that is practically inevitable. After all, these companies are working to develop novel treatments for barely understood diseases with highly complex and novel science. However, being aware of the challenges along the way can help emerging biotechs avoid devastating setbacks.

Although emerging biotechs face numerous challenges on their way to market, there are four key issues that highlight drug development in the biotech space. These include the competitiveness of the biotech and pharma industry, the possibility of unexpected complications, issues with finances, and the effect the team has on the outcome of projects.

SURVIVING IN A HIGHLY COMPETITIVE INDUSTRY

"At this moment, we are trying to develop treatments that haven't been defined, with science that has yet to be tested, to treat diseases that we are only now beginning to understand," Reinilde Heyrman, MD, Senior Vice President of the Medical Department at Medpace, describes the current state of the biotech industry.

Rising drug development costs, a steadily accelerating race to collect impactful data, increasing knowledge of the epidemiology of diseases, growing competition for suitable trial sites, and a generally crowded market, are all factors that shape the highly competitive landscape of the life sciences industry.

Although the numbers are still disputed, most people in the industry agree that the costs for drug development have greatly increased in recent decades, with the launch price of cancer drugs almost doubling over the last two decades[16][17]. The estimated cost to develop a single new drug can range anywhere from $161M to $4.5B, depending on therapeutic area[18].

These numbers show that a drug's failure can set a company back a long way. This is especially true for emerging biotechs, who often only have one or two compounds in development. If these are unsuccessful, the financial burden involved can be enough to result in the company's failure. Consequently, companies are constantly working to collect impactful data and increase their knowledge of the epidemiology of diseases.

Once the preclinical stage has been successfully completed, the race for finding suitable clinical study sites begins. Site selection can be a lengthy process, however, it is essential to the success of the trial. Sloppiness in deciding on the clinical trial location can negatively impact the outcome of a study. Selecting the wrong site can lead to poor patient recruitment and low-quality data, which can cause severe delays and become very costly[19].

FACING A HIGH LEVEL OF UNCERTAINTY

"Uncertainty is a habit of new things. We are developing treatments that haven't been defined, with science that hasn't been tested, for diseases we barely understand. Managing uncertainty and mitigating risk are part of the work biotech and pharma companies do."

- Reinilde Heyrman, MD, *Chief Medical Officer, Medical Department*

Within this competitive industry, emerging biotechs face a great level of uncertainty. There is a high likelihood of unexpected complications cropping up along the way. With only a small number of compounds in development, each step towards success and every failure are greatly amplified. Uncertainty follows emerging biotechs throughout the drug development process, starting at the root of scientific knowledge, from which the compound is based. As emerging biotechs often try to tackle unmet medical needs, they are moving in areas of science that have not yet been fully understood. This brings with it a high level of risk and increases the probability of failure[20].

In an environment that changes from day to day, emerging biotechs are also confronted with technical, financial, and market-related uncertainties[20][21]. They rely heavily on a complicated network of stakeholders, including large pharmaceutical and financial players. Failure to reach the predefined milestones in preclinical and clinical development can result in a loss of crucial funding[20].

CONFRONTED WITH FUNDING ISSUES

Funding is the lifeline of emerging biotech companies. The high costs of drug development force emerging biotechs to fundraise several times during the drug development phase. Whereas tech companies, for instance, can bring a product to market in a few months, biotechs need a number of years of spending before their product can even become profitable[18]. And even after all that time, the risk that the product will not succeed is extremely high[18].

Gaining funding at the beginning, predicting the correct budget for the clinical development program, and building a comprehensive strategy is therefore especially hard. "Investors tend to present funding once certain milestones are reached and data emerges. This can oftentimes present challenges to small and emerging biotechs in long-term development planning and execution," explains Brad Hansman, Vice President of Site Activations & Maintenance at Medpace.

If an emerging biotech fails to achieve its set goals or does not make a comprehensive plan, it risks losing its investors' trust[22]. Planning ahead and aligning the timing of fundraising with the different clinical development milestones is a tricky business and can only be achieved with the right team.

PUTTING TOGETHER THE RIGHT TEAM

Emerging biotechs can lack the necessary workforce to take their compound through all stages of drug development. "Emerging biotechs usually only have a small team of people, so recruiting and retaining talent is an ongoing challenge," says Heyrman. Additionally, the success of the emerging biotech can rise and fall with its management. As such, the management team needs to retain a good relationship with the company's shareholders. Not only does this influence later funding rounds, but it also affects the dynamics of the team. The management can benefit from the shareholders' expertise, so together they can build a team adapted to the fast-paced environment of the biotech industry[22].

The small size of emerging biotechs also means that a decision has to be made regarding the type of work that will be outsourced and kept in-house. "As drug development is multifactorial, it requires expertise in a number of focus areas, including chemistry, nonclinical, clinical, and regulatory," Hansman explains. "Smaller companies without these resources are left to rely on consultants. This can lead to misalignment of the strategy and a lack of continuity in execution across the program."

CONSIDERATIONS FOR EMERGING BIOTECHS: THE CRITICAL TIME BETWEEN PRE-IND & FIRST IN-HUMAN

Although emerging biotechs face the challenges discussed above, there are several steps they can take to mitigate the associated risks. As a biotech's drug development program not only includes the in-house team but also external experts, advisors, investors, and other partners, it is crucial that the biotech develops an overall strategy that can be followed and understood by all of the shareholders involved.

DEFINING & ADHERING TO A STRATEGY

"What I often see is a desire to run before one can walk. There are different phases in drug development, and over the years, these phases have been tested over and over. So, there is evidently a good reason why these phases exist."

- Reinilde Heyrman, MD, *Chief Medical Officer, Medical Department*

By defining a strategy early on in the development process, emerging biotechs can mitigate potential risks and challenges. Foreseeing these can help the company to act before they arise.

Therefore, while developing their strategy, biotechs should always keep their end goal in mind, whether that is a certain fundraising round or the registration of the compounds[23][24]. "Building a strategy and executing it with an end goal in mind will allow for marketing in the desired patient population, for the desired indication, at the desired dosing regimen," says Hansman.

Furthermore, defining a goal will help the research team understand and anticipate the different inflection points during drug development[23][24]. "Biotechs need to be very smart," says Heyrman. "They should think carefully about what they can accomplish, what kind of data can be acquired, and what answers need to be provided before moving to the next phase. This also requires a certain degree of patience."

Patience is a keyword. While many emerging biotechs may feel the urge to skip certain stages of the project to save time and money, the careful step-by-step acquisition of data lowers the risk of failure and decreases the chances of having to go back and revisit specific experiments, which can cost time and money.

"In the end, it is not only about how well the strategy is defined within a company, but also how well that company is capable of adhering to that strategy," says Heyrman. "After all, to be successful it is not sufficient to set up a plan, it also requires a certain discipline to follow that plan."

"It is extremely important that emerging biotechs give themselves sufficient time in the planning stages. So many biotechs put themselves under time pressure and rush during the planning phases, developing a suboptimal protocol that then requires multiple revisions. This wastes time, energy, and money."

- Nicholas Alp, MD, PhD, FRCP, FACC *Senior Vice President, Medical Department*

Taking enough time to develop plans and protocols is essential. During the planning stage, companies should make sure their protocol is scientifically focused and operationally feasible. They should discuss the protocol and clinical development plan with the right authorities, and consult subject matter experts on the proposed scientific and operational strategy.

Heyrman adds: "What delays studies is actually the pharmaceutical development. Biotechs should ask themselves what is needed for a clinical trial? Do they have everything they need so the trial can start on time? Is the clinical supply available? Does the product have a long enough shelf life so that if there is a slight delay, it can still be used for the trial? All of these questions need to be asked during planning stages to anticipate and mitigate risks to save time."

Moreover, clinical development plans should be compared and carefully checked with the preclinical work. Here, it is important to make sure that the animal data can be compared with and extrapolated to human data. "The rule is to fail early and fail cheaply," says Heyrman. "If there are any signs from the animal data, or from the literature for this class of compounds or for this kind of disease that there is a risk to humans, then the right experiment needs to be set up in humans allowing for a decision to go forward with the compound or not." Including a scenario for unexpected findings in the clinical development plan is therefore essential.

WORKING WITH THE REGULATORY AUTHORITIES

Another way for emerging biotechs to increase their chances for success is by starting a dialogue with the regulatory authorities early on in the drug development process, especially when developing advanced therapies[25]. This is an important step in the process, because going down the wrong path can waste time and money.

Therefore, in order to communicate with the FDA or other regulatory bodies, emerging biotechs should have a realistic understanding of their project's capabilities and limitations, including those technical areas that fall under specific regulatory considerations[25].

As more and more new disease areas arise, the development of novel medicines increases. However, while regulations are slowly adapting to these new medicines, they may not be adapting as quickly as the science and the understanding within the scientific world. This makes working in a regulated environment essential[21]. For companies with no regulatory experts in the team or who are new to the process this can be quite challenging. Here, an experienced, global partner with intimate knowledge of the necessary regulatory frameworks is vital.

FINDING A SUITABLE PARTNER

"The right CRO can offer a full partnership rather than an 'extra set of hands'. Given the limited resources of smaller and emerging biotechs, this can be crucial for the success of many areas of drug development."

- Brad Hansman, *Vice President, Site Activation & Maintenance*

Teaming up with a suitable partner and finding the right lab space, sites, and experts is crucial to increasing chances of success for emerging biotechs. A Contract Research Organization (CRO) can help these companies to maximize internal resources, accelerate development processes, and drive efficiency[26]. While emerging biotechs are focused on their next funding round, for instance, the CRO is responsible for running and overseeing the current study. A transparent collaboration between the two can enhance the design and execution of trials.

A PARTNER SHOULD HAVE THE FOLLOWING KEY STRENGTHS...

COMMUNICATION

The relationship built between a biotech and its CRO partner must be built on a foundation of trust. As emerging biotechs are relatively small, they need to be able to rely on their partner to execute studies almost independently while they focus on other issues[27]. To maintain a high level of independence, the emerging biotech should make sure that it communicates openly and the CRO has understood its compound strategy and its goals.

When scouting for a partner, the emerging biotech should ask itself whether a collaboration between the two teams can work. "Find a partner who will not deprioritize you because of your small size or limited immediate pipeline," says Andrew Masih, Vice President of Clinical Trial Management at Medpace. "Then, form a collaborative relationship with key individuals at your CRO and ensure that they are invested in the science of your products as much as you are."

Heyrman agrees: "Make sure your CRO is large enough to conduct the program and yet small enough to care and understand that a ten-person company and the compound matter in their business as well."

Overall, **a CRO partner should feel like an extension to the emerging biotech's team.** With the help of a dedicated project manager, who works as a constant point of contact between the two teams, transparency and a solid organizational structure can be maintained.

EXPERIENCE

"Select a partner that suits your strategy," says Hansman. "Challenging science coupled with complex regulatory frameworks require an experienced CRO. Selecting the appropriate partner with drug development expertise and regulatory experience is crucial to ensure robust study designs to facilitate efficient clinical trial execution, impactful agency and site interactions, and regulatory submissions."

When choosing a partner, emerging biotechs should make sure that the CRO has the right experts to support them throughout the drug development process[27]. The CRO's experience and understanding of the science should also be reflected in past completed projects[12]. In fact, scientific expertise will also show whether the CRO will prioritize the emerging biotech's product development and support it throughout the drug development process.

"CROs should also have experience in the necessary therapeutic areas," Hansman adds. "It is critical to have advanced knowledge of the disease, endpoints, sites, patient access, and so on. Drug development expertise can further help the development of regulatory strategies and documents, as well as facilitate impactful authority interactions allowing for accelerated clinical development and authorization."

FLEXIBILITY

"One of the things I have learned over the years is to be open-minded," says Heyrman. "It is very important not to desperately stick to the path you're on, but to think of alternative scenarios in case things don't work out the way they were planned. Ask yourself: What is your backup plan? What is the backup plan for your backup plan?"

In a continuously changing and challenging industry, flexibility is incredibly important[27]. This also includes the flexibility of a partner. **A CRO must be able to help an emerging biotech find solutions to issues and adapt to unexpected problems.** "Find a CRO that develops proactive contingency plans versus reactive ones that include backup sites and even backup countries," Masih adds.

Moreover, choosing a partner who is a full-service provider versus a functional provider — where you choose services à la carte — can increase the probability of success. When your CRO can fully engage with its medical, regulatory, and operational teams and work under a single set of standard operating procedures, you should expect higher levels of quality and efficiency.

In a full-service approach, all services are coordinated under one roof, providing an accountable platform that reduces the need for duplicate management oversight. The more partners involved, the higher the chance for conflicts in the drug development process. This can impact costs and milestone success. The CRO can help strike the balance of disciplined execution and flexibility.

RELATIONSHIPS

For an emerging biotech it can be hard to select the right sites and get in touch with suitable key opinion leaders (KOLs)[24]. **The right CRO partner, on the other hand, will have well-established and recent relationships with sites and KOLs.** Furthermore, a partner should have a practical approach to recruiting, such as knowledge of sites with the right patients and the right mix of KOLs, as well as access to real-world global data[27].

"For the foreseeable future, clinical trials will continue to rely on motivated principal investigators (PIs) to recruit study participants, ensure their well-being and safety, and to diligently execute the study protocol," says Nicholas Alp, M.D., Ph.D., FRCP, FACC, Senior Vice President, Cardiovascular, Medical Department at Medpace. "PIs are the linchpins of clinical research, and nothing happens in a study without their buy-in. Establishing and nurturing relationships with these key professionals should be a core competency of a CRO partnering with biotech."

GOVERNANCE

Finding the right balance between structure and action is crucial in a drug development partner, as too much structure results in a loss of time and resources. Here, it is important that the CRO has a streamlined decision-making process[27]. "Look for a CRO that empowers its project management team to focus on study milestones rather than revenue generation, and ensure that the CRO leadership is fully engaged with your study and makes it their priority," Masih adds.

THE COLLABORATION MOMENTUM OF MODERN BIOTECH

"Work in close collaboration with your CRO, invest in them, give them knowledge of the development program. Knowledge is empowerment. Keep things as transparent as possible, involve all key stakeholders in processes that affect them, and work collaboratively."

- Andrew Masih, *Vice President, Clinical Trial Management*

By 2023, an estimated 49% of clinical development will be outsourced to CROs, representing a 12% increase in market penetration rate since 2018 [28]. The global CRO market is expected to reach a value of $87.7B that same year[28]. These figures are unsurprising as small and emerging biotech companies struggle with looming costs and the pressure to accelerate time-to-market while expanding their pipelines, keeping up with novel scientific discoveries, and improving drug efficacy and safety[26].

With their expertise in clinical research and design, a network of experts, KOLs, sites, and investments in the latest technologies, CROs can support emerging biotechs during the drug development process[26]. Moreover, while CROs work on the organization and execution of the various studies, emerging biotechs are freed to focus on other pressing issues, such as collecting more funding and reaching different milestones.

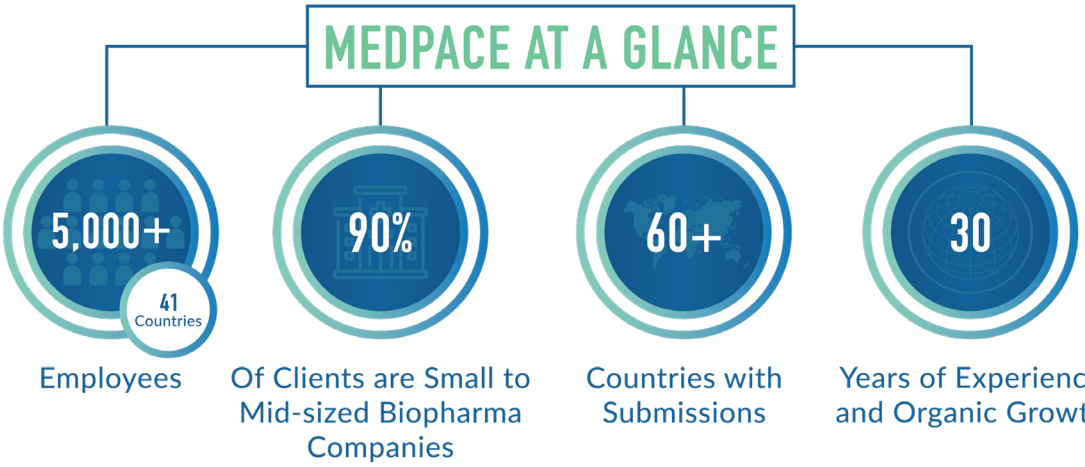
Although drug failure rates remain very high, the collaboration between emerging biotechs and CROs will increase the chances for successful drug development[29]. CROs can help mitigate risks by anticipating possible pitfalls and using their experience to navigate emerging biotechs through the complex processes of drug development and regulatory affairs[29]. No doubt, collaborations within the biotechnology industry will be increasing in the future.

By 2023, ~49% of clinical development will be outsourced to CROs

Representing 12% Increase in market penetration since 2018

In parallel, the global CRO market is expected to reach $87.7B in the same year

THE MEDPACE SOLUTION



As a top-10 CRO, Medpace's mission is to accelerate the development of safe and effective medical therapeutics worldwide. The company has grown organically over the past 30+ years, ensuring the stability of leadership, processes, technology, and expertise. At the center of their expertise lies a unique culture that fosters a partnership atmosphere, important for emerging biotechs with limited resources and sometimes limited experience.

"What is unique about Medpace is that we have a real passion to bring new therapeutic modalities to patients in need," says Heyrman. "We only work where we are confident that we can truly add value. All of our executions start in the medical science. We bring with us a sense of responsibility and ownership. We really want to be the right partner, the seamless extension of the sponsor team, to help them get their new therapeutic modality to market."

Medpace's full-service capabilities include extensive expertise in defined therapeutic areas that promote better trial designs and the acceleration of clinical development. The company's team includes regulatory experts, who can support emerging biotechs in all issues related to the regulatory authorities, be it communication, document creation, or filing.

Furthermore, Medpace's global reach and experience is crucial for navigating cultural and regulatory differences across countries. This is especially important when it comes to advanced therapies and genetically modified organisms where complex processes are involved and there is a lack of harmonization across regions.

"We have the culture and the organizational structure to quickly address unexpected issues. Additionally, our foundation in the medical sciences and our sense of responsibility and ownership gives biotechs a meaningful advantage," Heyrman adds. "Together with the sponsor, we are constantly striving to reach important milestones. This kind of partnership allows us to execute better; it also sets us apart."

Medpace is committed to **Making the Complex Seamless™** by providing uncompromising commitment to your clinical research and the highest level of ethical standards and performance, which translates to executing your trials on time, on budget.

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