

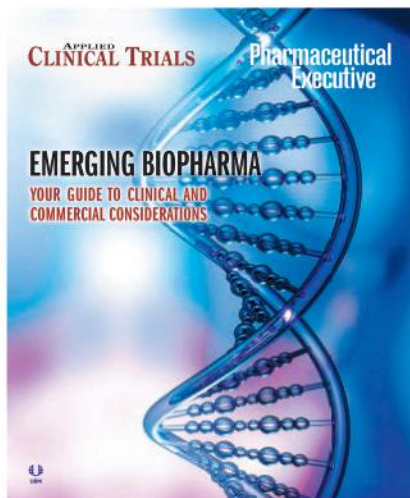


**APPLIED
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Pharmaceutical
Executive

EMERGING BIOPHARMA

**YOUR GUIDE TO CLINICAL AND
COMMERCIAL CONSIDERATIONS**



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Winner for
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Pharma and Biotech Markets

Peter Young

Mostly sunny, but challenging to forecast

For most of the last 10 years there has been a lot to be happy about in the pharma and biotech industry. The number of new drugs approved and under development escalated for both pharma and biotech companies. A host of new methods, such as immuno-oncology, CRISPR, personalized medicine, stem cells, and biologics have opened up a surge in productive innovation. We are beginning to see drugs that cure difficult diseases rather than just extend life, an extraordinary development. There have even been recent U.S. regulatory and funding changes that are intended to increase government funding and ease the drug approval process, although time will tell if the actual results match the intent.

The access to equity capital and the valuations of pharma and biotech organizations in the public and M&A markets soared until the end of 2014, in part because of these positive developments.

Since then, the innovation successes have continued, but there have been times when heavy clouds have appeared in terms of the stock market, access to capital, pricing controversies, and uncertainties around the ongoing structural changes in a number of the major markets such as the U.S. and China. There also was a slowdown in FDA drug approvals in 2016 in the U.S. with only 22 approved, which was troubling, but now appears to have been temporary.

Share prices and public valuations have been volatile since late 2014, with industry uncertainties and the drug pricing controversies to blame. Public biotech shares were hit particularly severely, and as a result, the IPO market cooled off in the second half of 2015 and plunged in 2016. Secondary offerings were strong in 2015, but also fell precipitously in 2016. This created a difficult equity financing environment for biotech companies, which, in turn, limited the choices available to biotech firms to continue to fund their companies. This contributed to a surge in M&A activity in 2015 and 2016 as

many biotech companies had to sell their companies earlier than they would have liked, often just after they achieved certain clinical trial milestones.

The rest of this article will provide the data behind these historical observations through the end of last year, but will go on to explain what happened in the first half of 2017 and what we expect for the rest of the year and beyond. We will also share our view of the implications of these trends for decisions being made by senior executives and investors in the pharma and biotech industries.

Pharma equity market performance

During 2016, the equity markets plunged in January and February and then recovered in March. Global markets saw a drastic dip again in late June in the wake of the Brexit decision, but quickly recovered. After the U.S. Presidential elections, the markets rallied strongly.

As a result, 2016 saw the S&P 500 increase 11.2% from the beginning of the year and the FTSE 100 increase by 17.2%.

In contrast, the Young & Partners (Y&P) pharmaceutical indices did not do well as a group. The Y&P U.S. Pharma index increased, but only by 6.0%. The rest fell. The Y&P European Pharma decreased by 14.6%, the Y&P Specialty Pharma index by 20.5% and the Y&P Generic Pharma index by 28.3%. As a result, there was a decline in the public valuations of ethical pharma, generic pharma, and specialty pharma companies in the West.

Clouds of uncertainty around the pharma industry were a heavy contributor to the decline, such as the negative comments about the industry during the U.S. presidential elections and the very visible and damaging pricing controversy.

The industry fared better in the first half of 2017. The global equity markets performed moderately well, with the S&P 500 increasing 7.3% and the FTSE 100 by 1.9%. This time, the Y&P U.S. Pharma

and European indices did better than the market, increasing by 8.5% and 14.6%, respectively. The Y&P Specialty Pharma index also increased, but only by 4.6%.

Only the Y&P Generic Pharma index did poorly, decreasing by 4.3%. The poor performance by the generic companies has been driven by their difficulties getting new volume and by intense pricing pressure.

Pharma equity financing and M&A

Equity issuance during 2016 equaled \$16.4 billion versus \$32.7 billion for all of 2015, a drop by about half. Part of the reason was the reduced M&A volume that dampened the need for equity. However, it was also due to the volatility of the equity markets and the negative sentiment about the biopharma industry.

There were only eight pharmaceutical IPO's in 2016. During 2016, 44 M&A deals were completed worth \$120.5 billion versus 58 deals completed worth \$201.5 billion in 2015. Although these were healthy numbers, they were a major decline from 2015.

Part of the problem was the sparsity of mega deals. Only two large deals were completed, the \$31.0 billion acquisition of Baxalta by Shire and the \$40.4 billion acquisition of Allergan's Generics Business by Teva.

The rationale for deals remained the same as pharma companies seek to strengthen their product portfolios, replace pending revenue losses from patent expirations, and restructure their business portfolios.

So why the dampening of M&A activity? Three of the principal reasons were the loss of tax inversions as an alternative for U.S. drug companies, the negative publicity around drug pricing, and the political uncertainties associated with the U.S. presidential elections where the drug industry was a target of all of the candidates.

As of December 31, 2016, the value of the deals announced but not closed was \$4.4 billion (15 deals), a very modest number in terms of dollars, but a solid number of deals. In contrast, the pipeline of deals announced but not closed at the end of 2015 was \$240.4 billion (16 deals), but many of those deals did not close and the biggest failed deal was the massive Pfizer attempt to acquire Allergan.

How has the M&A market fared thus far through the first half of this year? During the first half of 2017, only 13 deals were completed worth \$42.2 billion versus 44 deals completed worth \$120.5 billion for all of 2016. The majority of this dollar volume was Johnson & Johnson's acquisition of Actelion. On an annualized basis, this was a dramatic decrease in both the number of transactions and the total dollar volume and a continuation of the slowdown that started last year.

Further, as of June 30, 2017, the pipeline of the deals announced but not closed was only \$9.2 billion (12 deals).

Biotech equity market performance

As we indicated above, 2016 saw the S&P 500 up 11.2% from the beginning of the year and the FTSE 100 up by 17.2%. Most

of our biotech indices did poorly. The Y&P Large Cap Biotech index decreased by 14.6%, the Y&P Mid Cap Biotech index decreased by 5.2%, and the Y&P Small Cap Biotech index increased by 10.4% in 2016. Much of the blame was due to the negative publicity around drug pricing.

This year we are seeing a major turnaround. During the first half of 2017 the global equity markets performed modestly well, but the Young & Partners Large, Mid, and Small Cap Biotech indices performed even better, increasing by 12.1%, 24.6%, and 50.6%, respectively. This was a welcomed improvement over the poor performance overall in 2016.

Biotech equity financing and M&A

Equity issuance in 2016 fell significantly with 126 equity offerings worth \$8.7 billion completed compared to 206 offerings worth \$20.1 billion in 2015. In 2016 only 26 IPOs were completed for a total of \$1.9 billion in new equity, well below 2015 when 61 IPOs were completed totaling \$5.3 billion. The IPO market was frozen for all but the strongest IPO candidates.

On the bright side, equity issuance in first half of 2017 totaled 95 offerings worth \$8.4 billion. This was a significant pick-up in pace on an annualized basis compared to the 124 offerings worth \$8.7 billion completed in 2016. Although still less than the peak volumes in 2015, it was a vast improvement over the severe slump in 2016.

On the IPO front, the recent news is partially positive. In the first half of 2017, 20 IPOs were completed for a total of \$1.5 billion. On an annualized basis, this is well above the weak 2016 (26 IPOs totaling \$1.9 billion were completed during the entire year). We are not experiencing the frothy IPO environments of 2014 and the first three quarters of 2015, but we have pulled partially out of the 2016 slump. This has provided relief for some of the private biotech companies struggling to raise funds.

Biotech M&A activity has almost always been modest historically, with small spurts of activity from time to time.

In 2016 there were 42 biotech M&A deals completed worth \$19 billion compared to 31 deals worth \$19 billion in 2015 and 28 deals worth \$13 billion in 2014. The number of deals and the dollar volume increased significantly. This increase has been fueled by the pharma companies and their need to fill product pipelines and by the financial squeeze facing biotech companies due to the slowdown in IPOs and public secondary offerings.

Sealed off from high valuation equity offerings, the biotech companies were less fortunate in 2016 compared to the period from 2013 through the first half of 2015 when they were able to raise money at high valuations. In many cases, the biotech companies were not able to go public at all. As a result, in 2016 the biotech organizations who were in the midst of high-cash consuming Phase II and Phase III clinical trials, were forced to either sell or to partner in order to deal with their shortage of cash.

However, the pipeline of deals slowed significantly towards the end of last year. There was a major increase in geopolitical

uncertainties related to the biotech sector. The U.S. Republican Party's repeated vow to repeal and replace Obamacare, uncertainties around potential changes in tax laws and rates in the U.S., and the pricing controversies surrounding many companies such as Mylan, Mallinckrodt, and the industry as a whole all contributed to a slowdown in M&A activity.

This slowdown continued in the first half of 2017, with only 16 biotech M&A deals completed worth a mere \$2.8 billion. The two largest deals were the acquisitions of CoLucid and Ogeda. This was a major slowdown on an annualized basis compared to 2016 when, as mentioned before, 41 deals worth \$19 billion were completed. The 2016 totals were driven by six deals that exceeded \$1 billion in value.

Not surprisingly, the pipeline of biotech deals as of June 30, 2017 was extremely weak at only \$0.9 billion (five deals).

Outlook: Pharma

The business outlook for pharma companies will continue to be positive in terms of drug development, with promising drugs in the pipeline. The industry's trajectory in drug development innovation and productivity, directly and indirectly through the biotech industry, is strong and will continue to be strong.

There was some concern about the drop in FDA approvals last year, but activity picked up considerably in the first half of 2017 and there is a push to ease the FDA approval process in the U.S. In addition, the FDA announced in late June that it plans to promote drug competition, including expediting the reviews for generic drug applications. This will be helpful to the generic drug companies, but potentially harmful for the ethical pharmaceutical companies.

Pharma companies will continue to adjust their business models and strategies as the environment around them changes and new technologies are discovered. We fully expect big pharma to continue to pursue radical structural changes to shift the nature and quality of their business portfolios.

Specialty pharma companies will partner, license, and acquire to maintain the strength of their overall business portfolios and scale. However, many of these companies are under attack around the drug pricing issue and some are finding that their orphan drug strategies have limitations in terms of insurance company reimbursement policies.

Young & Partners expects Pharma M&A activity for the rest of 2017 and beyond to be relatively weak, a continuation of the relative weakness experienced in 2016. The shutdown of the large inversion deals has been and will be contributed to the dollar slowdown. However, volume will still be significant, driven by restructuring and strategic needs of the pharma companies and the residual impact of what was a feeding frenzy. Pharma companies will continue to acquire to enhance their product pipelines and strategic thrusts, while selling off non-core businesses.

The need to fill the shrinking drug pipeline will also fuel in-

licensing arrangements, partnerships, and joint ventures with biotech companies and other pharma companies.

Outlook: Biotech

The development capabilities of biotech companies have been and will continue to be positive overall. Although there will be successes and failures by individual companies, biotech companies have demonstrated their ability to develop new drugs at a faster pace than the larger pharma companies.

The stock market favored biotech companies for a number of years, but that sentiment weakened starting in the second half of 2015 with a number of negative stories hitting the biopharma industry around pricing and other issues, impacting the IPO and secondary equity issuance volume.

We expect the recent moderate improvement in the stock market and equity issuance market to continue for the biotech industry with positive regulatory changes being discussed. This will help the stronger biotech companies raise equity capital, but we do not expect a near-term return to the frenzy of 2014 and 2015.

However, the biotech M&A market will continue to be subdued, even with the ongoing Pharma interest in building their drug pipelines. This is partly because partnering is an active alternative to M&A and partly because the equity issuance market has improved so that biotechs are not as desperate for cash...

Implications for senior management

For ethical pharma companies, there will continue to be a wide variety of tools to acquire revenues and pipeline drugs, but the valuations are challenging, particularly for promising drugs in late stage clinical trials and for companies with strong products. The challenge will be to pick the right overall mix of M&A, licensing, and partnering to accomplish corporate strategic goals and defend and deliver shareholder value.

For biotech companies, public and private, the future is exciting from the drug development side in terms of the drug approval environment and innovation, but mixed with regard to private funding, IPOs, secondary equity financings, and M&A fronts.

The key for biotechs will be to properly assess their cash flow requirements and to create and execute a flexible financing/M&A plan that properly assesses how much capital and at what price the various alternatives will give you, whether it is private placements, partnering, IPOs and secondary offerings, royalty monetizations, or sources of non-dilutive financing.

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Real-World Data and Emerging Biopharma

How lean organizations can generate time and cost savings in drug development by leveraging real-world data

Across the biopharma industry experts are touting the value of using real-world data in drug development programs, and rightfully so. When clinical teams incorporate data from electronic health records (EHRs), patient registries, prescription records, and other real-world sources, they can achieve numerous benefits, such as making better protocol designs and speeding patient recruiting. Real-world data can also play a pivotal role in proving the value of a new drug through long-term efficacy and safety studies conducted under pragmatic real-world conditions. The 21st Century Cures Act is spurring this trend, by calling on FDA to support approval of new indications and label expansions through broadened use of real-world evidence.

The implications of these benefits are especially important for emerging biopharma (EBP) companies whose drug programs now make up more than 70% of the global industry pipeline.¹ EBPs are lean organizations with limited resources to support development of assets that often focus on difficult-to-recruit patient populations. This puts enormous pressure on them to achieve the next milestone or value inflection point as quickly and efficiently as possible.

Leverage data to efficiently find patients

Developing a real-world data strategy that integrates patient and investigator-level data can ease these pressures, allowing cash-strapped companies to extend those resources and generate more robust trial initiation plans. Yet EBPs face obstacles in using real-world data, placing them at a disadvantage in leveraging these tools.

Due to the nature of their organizations, EBPs typically don't have in-house expertise to identify all real-world data sources relevant to their clinical program. They may also lack the technology to access and analyze these data sets, or the systems needed to integrate these data into their clinical data sets, a critical piece to fully leveraging and making insight-driven decisions regarding their asset's utility and value.

These kinds of insights don't just reinforce gut instincts about research programs. They can help make decisions that translate to significant time and costs savings, and in some cases, it may mean the difference between success and failure of a trial.

For example, in a recent Irritable Bowel Disease study supported by QuintilesIMS, the research team initially found two sites each with access to more than 350 potential patients. With insights from additional real-world data sets, the team discovered that one site had more than 100 patients who met a specific treatment criteria, while the other had just 16. These real-world data helped guide the research team to avoid these sites that had little chance of meeting its enrollment goals, redirecting them to sites more likely to enroll. The overall im-

pact: saving downstream time, issues, and costs in the sponsor's trial.

We've also seen EBPs use real-world evidence to support clinical trial data for drug approval or label expansions efforts. This added evidence enables them to answer regulators' questions and potentially avoid having to conduct additional clinical research as part of the approval process.

For EBPs to overcome their data obstacles and make the most of real-world evidence, they need to spend time early in clinical development working with their partners or CROs to determine the broader set of data, aka 'evidence' available supporting their research, and where and how these existing data sources can be leveraged to advance their assets and drive value for their organization. Creating this 'evidence generation plan' early on ensures the development strategy is inclusive of all data needed to substantiate the product's utility for all stakeholders, including payers, regulators, and health systems.

The application of real-world data in biopharmaceutical development is still relatively new, giving EBPs an opportunity to establish themselves as leaders in this space, and to gain an edge on the competition. But this opportunity will be short lived. With new technological and data initiatives, and a growing interest by FDA and other regulatory bodies to work with sponsors in crafting strategies using this data, expect to see rapid adoption of these real-world data strategies across the clinical research lifecycle.

Amy Sheridan is Sr. Director and **Laura Marquis** is VP and Global Head, both with Emerging Biopharma, QuintilesIMS.

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Video

1. David Thomas, CFA and Chad Wessel, Emerging Therapeutic Company Investment and Deal Trends. BIO INDUSTRY ANALYSIS. BIO International, March 2016.

Funding ‘Crazy’ Ideas and Building Extraordinary Companies

Kristina Burow

The secrets VCs look for when making investments

The trick is to analyze the potential of the big scientific ideas behind a biotech company's platform, and one crucial factor is “attractable biology.” For example, with Vividion Therapeutics, a San Diego-based biotech, the big proteome idea was appealing to investors because it meant you could look across the proteome, identify active sites, and work in areas of biology. “Undruggable” targets, or difficult-to-drug targets, become attractable because suddenly the platform is transformed from difficult, near incomprehensible biology to attractable biology with clear chemical starting points that are easily modifiable. That is what makes for a powerful platform. Along with unlocking a novel target, it is also putting the investor on board a path to a drug. The ingredients for the investment deal—robust biology, robust chemistry, a highly experienced team of experts, and intellectual property—were all there.

Modern technology and approaches, together with understanding what exactly a therapy does before you bring it into Phase II clinical trials, enables significant risk reduction compared to 10 years ago.

Limited risk is a vital consideration. There's always risk to a biotech investment, but today's environment of drug hunting has the ability to reduce

that risk to a certain extent. Step one is defining the target of interest and correlating that target to the disease state. Being narrowly focused on exactly who the patient is, and being able to identify a therapy that modifies the disease in a specific patient population, reduces the potential for drug failure and program failure. Risk can never be completely eradicated because the investment proposition involves human biology. But modern technology and approaches, together with understanding what exactly a therapy does before you bring it into Phase II clinical trials, enables significant risk reduction compared to 10 years ago. The idea and capability to stratify patient populations and target therapies specifically to individuals and individual disease states has significant investor appeal.

Biotech groups can make themselves more attractive to investors as a consequence of working closely with contract research organizations (CROs). A revolution has taken place over the last decade—with academics that join early stage biotechs, obtaining access to low-cost sequencing, novel technologies like CRISPR, and better tools. Collaborations with organizations like WuXi AppTec have enabled biotech groups to push programs further and has put them on a much more stable footing before setting about licensing—with programs closer to a validated point.

Groups like Scripps have become increasingly flexible in the academics that they bring in and the way they work with the outside. For example, Receptos, a wholly owned subsidiary of Celgene, was started by three academicians, with two-thirds of the founders having pharmaceutical ties. These former pharma executives, who are now on the ac-

ademic side, unleash their knowledge to think creatively about next-generation drug discovery—combining great ideas and the power of being in an academic setting with the knowledge base of pharma.

Life sciences-focused venture capitalists (VCs), who are well versed in the challenges and complexity of the sector, first look at the science and then figure out how to build a strong biotech company. The key is to look at what the organization's science demands are and then build a company around that. It is possible to go from an initial meeting to an IPO in just 14 months—raising hundreds of millions of dollars. In other cases, for example, with the company Unity Biotechnology, five years, and \$2 million, were invested in establishing that the science was real and that the target and biology were druggable. The science led us to the company-building strategy. Now that Unity has matured, they have hired an experienced CEO, raised \$116 million in a Series B financing, have grown rapidly, and have reached the clinic.

Institutions have become savvier and are dedicating more resources to their facilities to help them to better think through how best to take great scientific ideas and turn them into actual biotech products.

Three elements have come together to create a really interesting time in start-up biotech investing. First, multiple technologies have advanced, lowered in price, and become more available. Second, academics are becoming more knowledgeable themselves about using these tools and technologies and are thinking three steps ahead about what these programs should look like. And, third, institutions have become savvier and are dedicating more resources to their facilities to help them to better think through how best to take great scientific ideas and turn them into actual biotech products.

We are also observing several major new trends. Those include biotechs with artificial intelligence and deep learning approaches, such as Grail, who are attracting significant investor interest. In Grail's case, a 140,000-patient observational study is planned—looking at very deep sequencing for each of those patients. A great deal of valuable information will be pulled from this—with big data emerging as a critical factor. Being able to draw correlations and pull information from that data will be highly important. There is also investor excitement in *in silico* approaches to drug discovery—an area that has considerable potential.

On the flip side, there are concerns about what will happen 10 years from now if groups like the NIH cut funding and if there is too great a shift toward peer asset-based academic research. It is important to the pipeline of drugs emerging out

of early-stage research that a significant number of novel scientific ideas receive funding—even if they are not validated.

To read a more detailed interview with Kristina Burow, please visit: wxpress.wuxiapptec.com

Kristina Burow is Managing Director at ARCH Venture Partners

Biotech CEO Viewpoints

Leaders from seven biotechs discuss trends, innovations, and scientific challenges their companies face in the smaller biopharma world.

Earlier this year, *Pharmaceutical Executive* moderated a discussion with CEOs from seven emerging biotechs to explore the prevailing issues and challenges facing the biopharmaceutical sector in 2017. Does true innovation—or the potential of new technologies and novel science in transforming medicine—still hold the trump card to opportunity in today's turbulent and uncertain healthcare, business, and regulatory climates?

PE: Are there ex-U.S. regions where you are seeing solid industry growth in the early stages of 2017?

JIM MCGORRY: When I think about growth within our area of esophageal cancer, it comes down to epidemiology. This disease is 10 times more prevalent in the Asian population. Food and diet in regions outside the U.S. and Western Europe is a contributing factor to a much higher incidence of esophageal cancer. Therefore, we are focusing on the Asian market due to the increased prevalence of the disease in those populations.

GIL VAN BOKKELEN: The epidemiology is definitely a big consideration when you are thinking about moving into a particular geographic region or about incorporating clinical activities in those areas. A region that I have been very impressed with and spent a lot of time in, is Japan. One of the thrusts of Abenomics is to invest more in healthcare and particularly innovative technologies like regenerative medicine. Japan, like a lot of other countries around the

world, is experiencing an unprecedented transition where we are seeing a massive expansion of the elderly segment of the population. A lot of people haven't really taken the time to assess what that is going to mean from a healthcare economic perspective.

The reality is that as we get older, we can spend eight to 10 times more annually on healthcare-related expenditures than we do when we are younger and healthy. Japan has the worst demographic profile of any developed country and probably any country, period. They recognized this because they've got a national healthcare system, and they started doing things that have created a much more favorable environment, designed to promote innovative healthcare solutions in the areas where they need them the most. Within the last couple of years, Japan has implemented new regulatory frameworks designed to expedite development, not just for regenerative medicine therapies but other forms of innovative therapies, which I think have a more broad-based benefit in terms of shortening the clinical development path, making it more concise, more efficient, and yet doing it in a way that protects and ensures patient safety and well-being.

If you can create better efficiency, which some of the provisions of 21st Century Cures Act in the U.S. are designed to do, and if other regulatory initiatives have the desired impact, you can get a shorter and less expensive development cycle. Ultimately that benefits everybody—the companies,

CHRIS ANZALONE, President and CEO, Arrowhead Pharmaceuticals: An RNA interference (RNAi) company focused primarily on hepatitis B and alpha-1 antitrypsin deficiency.

JIM JOYCE, CEO, Aethlon Medical: A clinical-stage organization that is advancing a therapeutic biofiltration device that has a specific affinity to bind circulating viruses and cancer-promoting exosomes.

CHRISTIAN KOPFLI, Co-Founder and CEO, Chromocell: Chromocell uses its Chromovert technology to use rare cells ideally suited for effective high-throughput screening. Chromocell's pipeline is currently focused on analgesics and rare diseases.

JIM MCGORRY, President and CEO, Biostage: Regenerative medicine company focused on esophageal cancer. The company's novel Cellframe™ technology is engineered to stimulate the body's signaling pathways and own healing process to regenerate and restore organ function.

GIL VAN BOKKELEN, Chairman and CEO, Athersys: Clinical-stage regenerative medicine company developing Multi-Stem®, a patented, adult-derived "off-the-shelf" stem cell product platform, for multiple disease indications in the areas of neurological, cardiovascular, and inflammatory and immune disease, as well as other indications where there is unmet medical need.

GEORGE YEH, Founder and CEO, TLC Biopharmaceuticals: Lipid-based formulation and scale-up for parenteral drugs using micelles and nanoparticles to optimize the pharmacokinetics of drugs for better efficacy and lower toxicity to prolong the product lifecycle of branded drugs.

DANIEL ZURR, Chairman and CEO, Quark Pharmaceuticals: Late clinical-stage pharmaceutical company in the discovery and development of novel RNAi-based therapeutics for unmet medical needs.

the patients, and the investors.

JIM JOYCE: One of the most challenging things that management of a therapeutic company faces is the question of what regions of the world are they going to pursue. In our case, we had opportunities to initiate human studies early on in India and other regions. The regulatory barriers were lower in those regions. There was never any assurance that the FDA was going to give us clearance to initiate studies in the U.S., so we focused on collecting data overseas. It was very valuable. That data got us to the point where the FDA approved studies for us to move forward and advance our technology in the U.S.

Then you have the dilemma of thinking about, "Well, am I going to focus on U.S. clinical progression?" If you are a publicly traded company, you have to evaluate and consider the market's long-term response to the path you choose. How is Wall Street going to value you? Some companies may choose to say, "We want to focus on early product commercialization"—a lower-barrier entry—and can be successful in doing that, with the plan of coming back and advancing things in the U.S. But then they find out that Wall Street starts to value them on a revenue earnings model once their product is approved overseas. And, thus, their post-approval shrinks to levels below that of when they were

progressing clinically.

It's a very challenging decision. It's a decision that most investors don't understand. You need to evaluate where the primary market is, what's the largest market, what is the reimbursement climate, and where the value is. If you are a company that is doing something that could attract large organizations that might want to acquire your business, if you are not advancing clinically in the U.S., there is probably not much interest. I have seen colleagues go overseas, never to be seen again. And I have seen companies here in the U.S. take therapeutic candidates through the FDA approval process and fail.

CHRIS ANZALONE: I disagree with one of the things you said. I think, dependent upon where in the world a company's clinical development is happening, you can still get a lot of interest from Wall Street and still be taken seriously from acquirers. It depends on where it goes. It's been our experience that the way the FDA is structured now, that—at least for us—there is little reason to do early stage clinical development in the U.S. It's much faster ex-U.S. It's easier for FDA to have it done ex-U.S. and then come back here for pivotal studies.

DANIEL ZURR: Nevertheless, if you develop a really innovative drug for an unmet medical need, if you don't get

FDA approval for the clinical studies, you will not go to a country like India. Getting U.S. approval is still the gold standard. You can conduct some studies outside the U.S. and return to the U.S. later. But if you want to get approval worldwide, you had better do it in the U.S. first.

GEORGE YEHL: We have trials done in Japan, China, Taiwan, Europe, and the U.S. I always tell people the fastest way is through the Taiwan FDA or the China FDA or through the NDA (new drug application) process with the U.S. FDA first. Because, with a lot of these other countries, there are not as many experienced reviewers, which can make the process very indecisive and go in circles.

PE: *Is the merging of different review departments within FDA a wish during a product evaluation—so that you don't have 16 people in the room, so to speak?*

McGARRY: The FDA is right to have a delineation of departments to regulate a device versus a biologic. This enables regulators to stay ahead of the technology and make an informed decision about the potential of the product.

The difficulty comes when the FDA evaluates products that address rare or orphan diseases. Today, there are thousands of orphan diseases identified around the world. With that in mind, there is an important social question: should we focus our efforts on treatments for just those rare dis-

If you are a publicly traded company, you have to evaluate and consider the market's long-term response to the path you choose. How is Wall Street going to value you?

— Jim Joyce, Aethlon Medical

eases or focus our efforts on treatments for broader disease states? This social question also applies as technology and big data change.

PE: *What are some of the main scientific challenges your companies face in advancing your technologies forward?*

ANZALONE: We have enough science to fill all of our lifetimes. It is translating that into clinical programs and then translating that into marketable products. We are at this amazing time in science where we can innovate extremely rapidly with animal models, *in vitro*, etc. But there is still this massive bottleneck, in part because it's complicated now to get into clinical studies, but also because of the capital necessary to support it.

CHRISTIAN KOPFLI: I couldn't agree more. There's plenty of science and technology out there. It's more about choice—where are you going with it? The reimbursement

factor is important as well. You go into something with big hopes, but very early on in the process, you have to consider the market outlook; does the product you are trying to develop really compare sufficiently above the what's out there? That may sound easy to do at first glance, but particularly in my company's area—pain, it's so broad and risk profiles come into play. The reimbursement aspect can also put you in a situation where you believe in that molecule or that therapy but just can't be sure whether it will get reimbursed or whether the insurer understands that it should be reimbursed.

VAN BOKKELEN: There is a lot of debate right now about how do you appropriately reimburse so-called curative therapies. Some of these are designed to be a one-time therapy that has a long-lasting therapeutic impact in a way that's not contemplated under the historical third-party payer reimbursement dynamic, which is “we are going to pay for you to take this pill for an extended period of time, or forever.”

To use some of the pediatric orphan indications, for example, where you can treat a child and cure a disease that might otherwise be progressive and debilitating, that has decades-long impact; but, yet, you've only got a small population and you still have the significant cost and development challenges to face. How do you figure out a reimbursement dynamic that's going to accommodate all of that? The reality is we still don't know. There is discussion going on between industry, third-party payer groups, and sponsors and innovator organizations like ARM and BIO to try to get to a better place on this issue.

ZURR: Developing an innovative drug, because of the state of biology today, is like going to a casino and just playing roulette. The rate of failure is still very high. It's true that there are more technologies, and from time to time, like in every science, you have one breakthrough, such as CRISPR/Cas9, for example, and that moves everything forward. There are certain drugs today that you have to test diagnostically before administration in humans. These are the directions that we're heading.

PE: *Given these dynamics, how would you assess the state of emerging research areas such as stem cells, regenerative medicine, RNA technologies, etc.?*

VAN BOKKELEN: I think that regenerative medicine, cell therapy and other advanced therapies, like gene therapy, are in a positive place right now. Contrary to a lot of the narrative out there, the FDA actually has significant knowledge and willingness to engage with companies and help give them guidance, much more than it did 10 or 15 years ago when this field was really just beginning, and in its early stages. This doesn't mean that everything operates perfectly.

But I think that if you look at the capital flow into regenerative medicine and advanced therapies over the past several

years, it's risen dramatically. There's a growing recognition and appreciation that this is one of those areas that could really transform medicine as we know it, particularly for some major problematic conditions where there are no effective solutions and no good current standard of care.

The challenge now in this space, as more of us are entering into late-phase clinical development, is to see those discoveries translated and see a few compelling cases go to the finish line. That would create a kind of tidal-wave phenomenon, if you will, pushing in the right direction. I think we are almost at that point.

ZURR: If you look at RNA, especially siRNA or microRNA, the antibody is part of the sophisticated immune system, which was discovered even before the innate, or primitive, immune system. And we now know the role that RNA is playing in our body. One of the biggest surprises after the mapping of the human genome was that we have almost the same number of genes as the mouse. So, what is the difference? The difference is the regulation of the genes—and RNA is the major regulator.

The human race is able to take the antibody, which is a part of our immune system, and manipulate it to produce efficient drugs for its own advantage. Similarly, we are going to

The challenge now in the regenerative medicine space, as more of us are entering into late-phase clinical development, is to see those discoveries translated and see a few compelling cases go to the finish line.

— Gil Van Bokkelen, Athersys

do that with the primitive immune system of siRNA. It's just a question of time. Once the first siRNA hits the market, you will see an avalanche.

PE: *What are the things your respective leaderships think about or do actively—on a short- or long-term basis—to reinforce or improve the industry's reputational component?*

McGORRY: As a small company, Biostage hopes to improve the reputation of the industry by focusing on innovative technology, making wise business decisions, and learning from our peers. We hope to continue to make a difference in patients' lives.

VAN BOKKELEN: The organizations that we might be members of, whether it be the Biotechnology Innovation Organization (BIO) or the Alliance for Regenerative Medicine (ARM), or others, they don't just include companies. In the case of ARM, it's also disease foundations, patient groups, a broad community of people that all want the same thing.

They want safe, effective medicines to be developed and made available, and, therefore, are working together. One of the ways in which you can do that and make it impactful is to utilize different vehicles and platforms. For example, through the use of video, you can tell a story to personalize and humanize just how debilitating or devastating a particular disease indication might be and how innovation can actually help address that.

So, part of this is just good, old-fashioned communication using sophisticated, new-age technology platforms to help us do that on a more effective and comprehensive basis. Because, frankly, that's one of the things we all need to be devoting a little bit more time and effort toward—to help the outside world understand just how important and significant the work that we're doing really is.

KOPFLI: I think we all need to use the new tools to effectively communicate. I believe that one of the problems we have is that people have misconceptions about the industry. One idea may be that the patient side become more active—patient advocacy groups and the doctors who use the products we develop. We are innovating, but we are also creating profits, and, thus, our message might not resonate as much. Maybe people that benefit from the innovative products can step up more and help us communicate the message.

McGORRY: Every company expresses patient interest in a different way, but perhaps we need more dedicated people working in this area. Patient-centric approaches to business, such as collaborating with patient advocacy groups, are critical. They help give the business a deeper purpose.

Are You Ready for Phase II?

Seth B. Forman, MD

Three signs that you are ready (and a few that you are not)

You did it. Your compound made it through Phase I. You were finally able to test the compound or IP (investigational product) on humans. Now, it's time to evaluate whether your compound is really good for anything or if it's just something that seemed to work really well in mice. In order to get the right answer, you must ask the right questions, then develop and execute a strategy that helps you get one step closer to market.

1. New pathway or me-too?

If your compound is a breakthrough pathway, then the best practice is to study the trial design for the most recent breakthrough compound. Mimic the design of that drug, not those of the "me-too." Refrain from setting outlandish or unattainable expectations. Superiority may not be necessary if your compound has advantages, such as dosing (QD vs. BID) or route (SQ vs. IV) biological superiority (humanized vs. chimeric), over the initial breakthrough formulation.

Set your primary endpoints similar, if not identical, to those of the pivotal trials of the initial compound. Let the sales and marketing teams differentiate the advantages.

2. How do I choose my sites?

You need a strategy. You need to be efficient. You need to spend your resources wisely. Here's why: you will be required to push 250 subjects through your 16-week, Phase II study, or 750 subjects through your parallel Phase III trials.

The traditional strategy is to cast a wide net and contract with 40 or 50 sites. Those sites include the below-mentioned factories, mills, dabblers, high turnovers, professors, performers, and Dr. principal investigators (PIs). You should be aware of these sites and how they operate; it's critical to your success.

The factory/mill

The factory/mill site will only enroll a small percentage of your subjects due to the physicians' lack of interest. These sites do not rely on any particular disease state to succeed. The quality of data will be adequate. The volume is hit or miss because these sites often contract with physicians in the community who are not entirely committed to clinical research. In these cases, the doctors are often conducting many trials in many disciplines.

Dabblers

The dabblers are the doctors who may have an interest in research or may see it as another revenue source. You know these site locations, and in most cases, they are not mature sites, but keep your eyes on these dabbler sites. They have the potential for becoming a performer. As you allocate contracts, you may want to give a new site a chance instead of going back to a poorly performing mill/factory.

The performers

You know these sites, too. They are must-have locations. These are your home-run hitters, your play-

makers. You will not close enrollment on time without these sites. Thirty-percent of these sites provide 70% of the data. Every sponsor in the same space wants their participation and wants them without competitive studies. They are expensive, but worth every penny. Get out your checkbook; it will be the best money you ever spent.

Dr. PIs

Dr. PIs are individuals who would like to be principal investigators and heard they can make money doing clinical research. They also heard that it wasn't much work. These Dr. PIs give you five minutes of their time at the pre-selection visit and even less time at the site initiation visit. Unfortunately, they always happen to be busy the weekend of the investigators' meeting. Yet, somehow, these sites made it on to your list of locations to consider. Should you? The answer is a resounding no.

These sites will enroll a subject or two, but the physicians will not know much about the protocol or the subjects. Are they worth it? Again, no. There's always a chance that one of these PIs could be randomly selected to participate in an FDA audit and who knows what he or she will say to the auditor. This isn't exactly the person you want speaking about your trial to the governing and regulatory bodies.

The high turnovers

As the name implies, this is the high turnover site. You'll know it because the person who filled out the feasibility study is no longer employed there. And you keep introducing yourself to new people every time you communicate with the site. Beware of this site. There is something systematically wrong with the management, and while enrollment may be satisfactory, the quality may not be acceptable.

The professors

You must contract with these sites. These are the "names" you need on these trials in order to validate all of the work every other site does. The university medical centers have their own institutional review boards (IRB). Their IRB must review your protocol.

The process of contracting the university-based medical center sites is long and painful. And your company will probably pay the highest overhead and cost per subject. The good news is that they routinely have very low enrollment and that also happens to be the bad news. You will not want to work with them, but your board of directors will force you to do so. If one of the "Professor" sites happens to also be a "Performer," avoid telling anyone in order to minimize competition for these sites.

3. How many sites do I need?

You need as few as possible. Ten-to-fifteen performers can get you to your enrollment number, especially if the sponsor

explains the aggressive strategy. The standard strategy is to align the study with many sites and set low expectations. You will get to your goal with more headaches, sleepless nights, monitoring visits, etc. It will be a lengthy, time-intensive endeavor and the human capital will be great. Also, there is greater potential for add-on sites midstream; however, these will be expensive and time-consuming since they must be brought up to speed.

The secret formula

Get all the performers you can. Add in a few dabblers. Use professors sparingly. This formula isn't intended to save you money. It will, however, economize your investment. You'll pay performing sites high fees, but it will be worth it. You'll have fewer headaches and a higher likelihood of being on or ahead of schedule and at market sooner.

Coordinating a clinical trial requires commitment, knowledge, dedication, and a stop at nothing mentality. You'll encounter numerous road blocks along the way, but with practice, patience, and persistence, you'll be able to successfully deliver a drug that could help more than just mice live a healthier life.

If you feel you are not ready or you need help, turn the page to read about outsourcing your clinical program.

Seth B. Forman, MD, is a principal consultant at Forsight Consulting, principal investigator with Forward Clinical Trials, and board-certified dermatologist and founder of Forman Dermatology & Skin Cancer Institute

Partner with a CRO? Consider This...

In pharma, 50% of R&D spend goes to outsourced contract research organizations and most large sponsors don't conduct all of their clinical trials in-house. What about emerging biopharma companies? What considerations should they weigh in the contracted CRO world?

The temptation to use uncontrolled, early, small studies to support further development of products may prove problematic for emerging biopharmaceutical companies, and these firms require both innovative approaches and rigor for success," according to an article posted earlier this year by *The New England Journal of Medicine*.

Small biopharmaceutical companies range in size from virtual companies with no commercial products and no revenue to those with only a few commercial programs, and they are becoming increasingly important as drivers of innovation in drug development, explained lead author Richard A. Moscicki, MD, Deputy Director for Science Operations at FDA's Center for Drug Evaluation and Research (CDER). These firms often encounter important challenges in designing and implementing clinical development programs.

Small companies use a variety of approaches to address these challenges, including the use of new technical platforms, the use of new formulations or technologies that enhance the actions of known drugs, and the use of trial designs that take advantage of the specific market they hope to enter. Other businesses develop products that are spun off from or licensed from large compa-

nies, according to Moscicki. But they can also run into problems navigating these issues, or operationalizing the trials, especially in areas of rare disease, where the small number of patients available for studies is an impediment.

Utilizing a CRO

Biopharmaceutical and medical device companies of all sizes frequently outsource one or more aspects of their clinical trials. Outsourcing relationships range from tactical to strategic level partnerships with contract research organizations (CROs) and auxiliary vendors such as central laboratories, software solutions, imaging vendors, and other services.

Medium-to-large sponsors usually have in-house staff conducting CRO and vendor oversight with the guidance of their own company's vendor selection and SOPs. Smaller companies typically do not have the resources to dedicate an employee or team of employees to this critical task. Employees at smaller companies are usually focused on discovery of new treatments and scientific innovation. But often the smaller biopharma companies have both limited finances and experience in clinical trial operations. Yet the importance of overseeing and coordinating ven-

dors and expertise needed for clinical trial success should never be overlooked.

Access to the expertise of CROs and other vendors enables sponsors to augment their resource on demand and without carrying the full burden of large departments of personnel. However, since the sponsor has the ultimate accountability over the compliance, conduct, and budget of the clinical trial, the sponsor must put in place mechanisms for oversight of the deliverables, including recording of adverse events, enrollment, expenses, and so forth.

Small sponsors frequently depend on external funding from venture capital, private equity, government grants, or larger sponsor partnerships. While all sponsors want to conserve resources and be cost-effective, small sponsors with limited and tenuous funding may take shortcuts to preserve financial resources. This can lead to shortcuts in vendor oversight and management, which may prove costly to the success of the trial.

Primary challenges for small sponsors

Experience has demonstrated that modifications to clinical trial plans are common. Changes may be simple modifications, such as clarifying instructions. Or they may be significant, such as modifications to the study design.

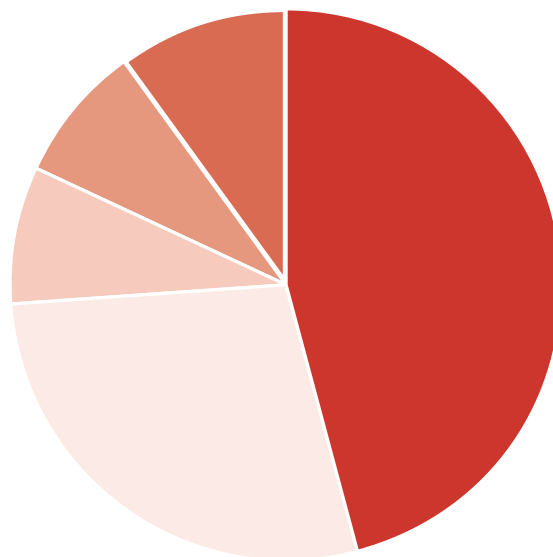
Even when progress is running smoothly with vendors, advice to shift strategies is sometimes introduced from newly hired C-suite executives, funding partners, and consultants. Even small shifts in direction for sponsors requires a thorough and robust process for change management and collaboration with all vendors.

Navigating change requires dialogue with each vendor to understand and communicate downstream implications. Change, even when it is positive, is also financially costly when vendors are not fully coordinated.

Breakdowns in communication and coordination foster most outsourcing challenges for small sponsors, according to a recent informal poll by Edgerton Data Consulting of five small sponsors. All five responders felt their low volume of work compared with the larger annual revenue of big CROs and vendors meant their trial did not get the priority and attention of bigger sponsors' trials. This lower level of attention manifested in several ways to the detriment of the smaller company's success such as:

- Not informed of study progress or risks to timeline and budget.
- Vendor's deliverables did not have adequate quality oversight. For example, one sponsor reported that the CRO's Statistical Analysis Plan (SAP) more closely resembled a SAP template than a draft of a study-specific SAP.
- Insufficient coordination and alignment with other vendors.
- Rigid vendor processes did not have adequate flexibility for the ever shifting priorities of the small sponsor.

FACTORS STIFLING PARTNERSHIP POTENTIAL



Cost Changes	46%
Staffing changes	28%
Protocol changes	8%
Technological changes	8%
Other*	10%

* Included changes in leadership/top management; lack of expertise; quality issues; and failure to meet timelines/deliverables

Source: *Applied Clinical Trials*/SCORR Marketing Survey, February 2017

The response breakdown from CROs and sponsors asked in the survey to cite "which factor can most negatively impact partnership?"

- Vendor staff turnover. It was not uncommon for sponsors to experience key vendor staff turnover multiple times in clinical trials of only six months.

However, these problems are not specific to smaller sponsors. In March, *Applied Clinical Trials* brought together experts in CRO and sponsor partnerships to provide their insights into this ever-evolving topic. With our survey partner, SCORR Marketing, we gained further insights into outsourcing partner attributes, benefits, and general attitudes toward outsourcing models from our audience. The full survey report is available here: <http://bit.ly/2mFuKdc>.

Our expert panel members included Kenneth Getz, Director, Sponsored Research Programs, Tufts CSDD, and Chairman, CISCRP, along with Murray Abramson, Vice President, Global Clinical Operations, Biogen; Phil Birch, Vice President, Innovation Strategy, Alliance Partnerships, ICON; Mitchell Katz, Head, Clinical Research & Drug Safety Operations, Purdue Pharma; and Andrew Schafer, President, Industry Standard Research.

At first glance, the list of challenges in outsourcing partnerships appeared long, as anyone involved with clinical trials outsourcing could imagine. Dissatisfactions from the CRO side included insufficient communication, poorly aligned processes, micromanagement, not involving CROs early in the process, and more. On the sponsor side, their dissatisfaction list included missed timelines, quality issues, and cost and out-of-scope amendments. And on both sides, staffing changes was identified as a major challenge (see chart on previous page). But as the discussion progressed, Abramson made clear the point that many issues are a symptom...and the diagnosis is inconsistency in the partnership implementation.

"Micromanagement is a symptom, the changing of staff is a symptom, the lack of trust and insufficient communication is both a means and a symptom. It is the inconsistency of the way things are implemented," said Abramson.

Consistency leads to success

According to Abramson, consistency at both the internal and external levels is important because it fosters predictability. And that provides an organizational environment that allows for innovation and improvement to occur. "It doesn't matter what sized organization you have—small, large, or mid-size, I think consistency is really important," said Abramson. "And it doesn't matter the approaches of outsourcing that a sponsor takes, it's the internal of what the sponsor does and what the vendor does."

To help build that consistency into the relationship, and in the organization across studies, Katz has developed a "CRO Playbook." The playbook is one consistent way to manage a study and is structured by function, describes Purdue Pharma's expectation from its CRO in those functions, and defines the roles and responsibilities of the sponsor and CRO. The playbook is continually refined or updated, used across CROs, and both the CRO and sponsor teams get the playbook.

"It has worked well for us," said Katz. "Part of the problem I saw on the sponsor side is that we weren't making our expectations clear, and if we did make them clear, it was only at the beginning of the program as opposed to throughout the program. [The playbook] is making it much easier, for different people coming in from different organizations to create and maintain consistency."

The ACT/SCORR survey respondents felt that strategic

partnerships have the most positive effect on large pharma, followed by large CROs. However, respondents also believed that the largest negative effect was on small-to-mid-size biopharma. This effect was also discussed with the *Applied Clinical Trials'* Editorial Advisory Board recently. With biopharma needing expertise to take their compounds further into clinical development before larger pharma comes in to develop further or license, they have found CROs prohibitively expensive. But some small-to-mid biopharma have found that by utilizing academic hospital networks, as well as targeted site networks, both possessing clinical trial expertise, has proven more viable.

The reasons behind the negative aspects of strategic relationships that our survey found could also be pipeline related. As Katz noted during the panel discussion, for smaller-to-medium sized organizations that do not have a large pipeline, it becomes more difficult to engage and initiate these long-term relationships because "these partnerships are only as good as the strength of your pipeline."

Tips for the smaller sponsor

However, take heart smaller sponsors. There are recommendations and keys at your disposal. For example, Edgerton et al suggest the following:

Initiate a foundation for success with vendor selection.

If sponsors don't have the expertise in-house, it is vital to hire a consultant to supplement your team in order to fully vet the vendors for areas of primary importance to your clinical development program.

In the Request-for-Proposal (RFP), ask the vendor about experience working with small sponsors. Also fully explore the vendor's process for keeping sponsors informed and managing changes in scope, quality control of deliverables, cost containment, and key staff transitions. Ask for examples for each situation.

Sponsors should request that the proposed members of the project team per RFP attend the bid defense as an opportunity to build engagement and set expectations with the team that will execute the project. Be wary of vendors that bring more staff to the bid defense meeting than sponsors have in the room. This may reflect lack of accountability for non-billable expenses, which ultimately are paid for by the sponsor. It may also demonstrate a lack of current work or lack of concern for the current responsibilities staff have that are interrupted by attending the bid defense.

Finally, but perhaps even more importantly, examine responses in context of whether there is a cultural fit.

Strengthen the foundation with a solid contract. The Scope of Work (SOW) generally lists the major tasks and deliverables in the clinical trial in the form of a matrix for who (vendor or sponsor) performs and approves each task or deliverable. Sponsors should modify this by adding timelines for quality deliverables. For example, if it is important to have

top-line trial results before a scheduled therapeutic area conference, agree on the number of days from database lock for top-line tables, listing and figures (TLF) delivery.

A similar expectation can be communicated regarding change-in-scopes.

- Define what constitutes real scope changes.
- Identify who can approve them and whether there are thresholds in cost level requiring additional approvals.
- Define how scope changes will be tracked.

For example, will each and every change have to be approved before implementation or can the sponsor and vendor agree on a level of cost that comfortably allows the vendor to work while the sponsor in good faith proceeds with scope change approvals? Also, be clear about who will be doing the work. If portions of the work are to be subcontracted by the vendor, the sponsor may want to provide approval first.

Maintain a strong foundation with oversight. There is fine line between effective vendor oversight and costly micromanaging. The sponsor's primary goal is to clearly communicate the path for mutual success. Vendors strive to comply with sponsor expectations and requirements. Sponsor oversight is one way vendors can stay on track and avoid uncomfortable conversations later due to miscommunication.

To accomplish this goal, the sponsor should provide an expert resource to serve as the sponsor project manager for all clinical trial activities. This resource can build engagement with the vendor team by attending and managing project team meetings and ensuring the sponsor team is an active participant in all aspects of the trial, such as development and approval of the protocol and all study plans. This includes case report forms and monitoring reports; user acceptance testing of tools such as the electronic data capture system; and critical review of study report, tables/listings/figures shells.

The panel members, based on their long history and success with strategic partnerships, were big fans of picking one model and sticking with it. Even if an organization prefers the functional service provider model, it is more successful, the experts say, to have one model with which to develop with a provider. From the panel members, the keys to developing the best CRO-sponsor relationship includes:

#1 Playbook: Develop a living document on the roles, responsibilities and expectations for both the CRO and sponsor. This document is updated, and shared when updated. It is also useful for training.

#2 Consistency: Choose one outsourcing model and stick with it. Use the playbook to provide the consistency in roles and responsibilities.

#3 Training: Training is essential, especially when the playbook changes. Training should also be tracked for compliance.

#4: Stamina: The knowledge that you are going to be in the partnership for the long haul and will be putting in the effort and investment to make it work.

Small sponsors who do not have a qualified internal resource to serve as the project manager to provide adequate vendor oversight should seriously consider hiring an experienced contractor to supplement their team. The goal of everyone involved is a successful clinical trial. Clear communication and effective coordination will ensure the best results possible.

This article is comprised of two previously posted articles at *Applied Clinical Trials*:

1. "The Case for Vendor Oversight for Small Sponsors," by Dawn Edgerton, MBA, RAC, founder of Edgerton Data Consulting; and Gerald L. Klein, MD, and Peter C. Johnson, MD, founders of MedSurgPI, a provider of medical affairs services, <http://bit.ly/2vE6Bs0>

2. "Outsourcing in 2017: Playing to Win," by Lisa Henderson, Editorial Director for *Applied Clinical Trials* and *Pharmaceutical Executive*, <http://bit.ly/2upi2ns>.

Four Steps to Commercial Launch Success

Specialty therapeutics—a staple of the emerging biopharma offering—require a different approach

As new drug launches proliferate in the hotly contested specialty therapeutic space, companies are finding that success is often pre-determined by actions that take place very early in the development and commercialization cycle. The vital drivers of success are (1) the quality and depth of interactions with three key influencers—clinicians, payers, and the patient—and (2) harnessing the powerful integrative effects of advanced, state-of-the-art technology infrastructure.

When Keryx Biopharmaceuticals launched its first compound, Auryxia, developed to control serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis, it devised an integrated four-plank strategy to accelerate its “go-to-market” launch date of December 2014. The strategy included a set of unique clinical trial designs as well as a key opinion leader (KOL) engagement blueprint designed to anticipate the likely actions of patients, payers, and clinicians as the basis for a truly differentiated positioning for Auryxia in the marketplace.

In addition, Keryx implemented new cloud-based technology to support the rollout. The technology gave the commercial teams access to customized information and supportive analytics that tackled one of the enduring flaws in traditional launch strategies: poor alignment among internal groups that are supposed to be working together to execute around a packed timeline, and the ability to react quickly to unexpected changes in the market.

Keryx CEO Greg Madison said the company began developing Auryxia 10 years prior, yet the road to getting the drug on the pharmacy shelf—the specific preparations to go commercial—was accomplished in just 10 months. Madison highlights four process innovations that the company applied to push this new medicine to market:

Keryx quickly learned that good data is not enough to see uptake in the market. Instead, success starts with intelligent clinical trial design in partnership with experts and clinicians who understand the needs of patients.

1) Build a critical therapeutic niche to address an unmet need

One of the first steps Keryx took toward commercialization was surveying the physician community to uncover the needs of renal disease patients. Keryx quickly learned that good data is not enough to see uptake in the market. Instead, success starts with intelligent clinical trial design in partnership with experts and clinicians who understand the needs of patients.

Keryx strategically designed its clinical trials so it could evaluate multiple comorbidities resulting

from CKD, but ultimately found that addressing a very specific unmet need within the CKD disease state would help set the company up for success and, most importantly, help patients. In this case, the niche disease area for CKD is hyperphosphatemia, or elevated serum phosphorus levels, which is often present among patients with end-stage renal disease (ESRD) since the kidneys are not able to excrete phosphate.

2) Differentiate and provide access

A core component of any biopharmaceutical company's marketing strategy is differentiation.

For Keryx, this meant honing in on a complication in a niche disease state for which there was an unmet need. Patients with CKD on dialysis often experience elevated serum phosphorus and iron deficiency. Auryxia was demonstrated to be an effective phosphate binder in clinical trials. In addition to effects on serum phosphorus levels, the pharmacodynamic properties of Auryxia has been shown to increase serum iron parameters, through systemic absorption, which is managed by the body's gastrointestinal regulatory mechanisms.

This differentiation didn't stop with brand attributes though; it was also important to consider payer and reimbursement strategies to ensure access to the product.

"We know access to medicines today is challenging, especially in the renal market. As part of our go-to-market strategy, it was imperative that we work with payers to provide patients with affordable co-pays," says Madison. This included a comprehensive patient services program that offers eligible patients financial assistance, with a dedicated case manager that provides personalized reimbursement support, including education about the co-pay and patient assistance programs.

It was also important to consider payer and reimbursement strategies to ensure access to the product.

3) Launch with a technology foundation that unites internal-external teams

Keryx began the process of building its commercial technology infrastructure with a simple goal: to enable its field teams to compile, interpret, distribute, and communicate site-relevant information to provide a differentiated customer experience. Keryx implemented Veeva Commercial Cloud, a single solution that pulls together customer data and analyzes and processes it to create a needs-appropriate platform for multichannel interactions with compliant content. Combined, the cloud-based technology captures all customer interactions across personal and non-personal channels, providing commercial teams with deeper insights about customer targets.

4) Go to where the talent is

Motivated multi-functional teams are required internally and externally to address the demands of the product on all fronts, including commercial, regulatory, medical, as well as technology. The company expanded New York-based operations to Boston, a hub of bioscience innovation, to attract and bring together a disciplined and seasoned talent pool capable of collaborating towards its product goals.

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