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Strong Culture Helps Jazz Beat the Odds

The path that led to Jazz Pharmaceuticals to be one of the hottest targets of acquisition
p. 20

BRUCE COZADD
Cofounder, Chairman, CEO
Jazz Pharmaceuticals

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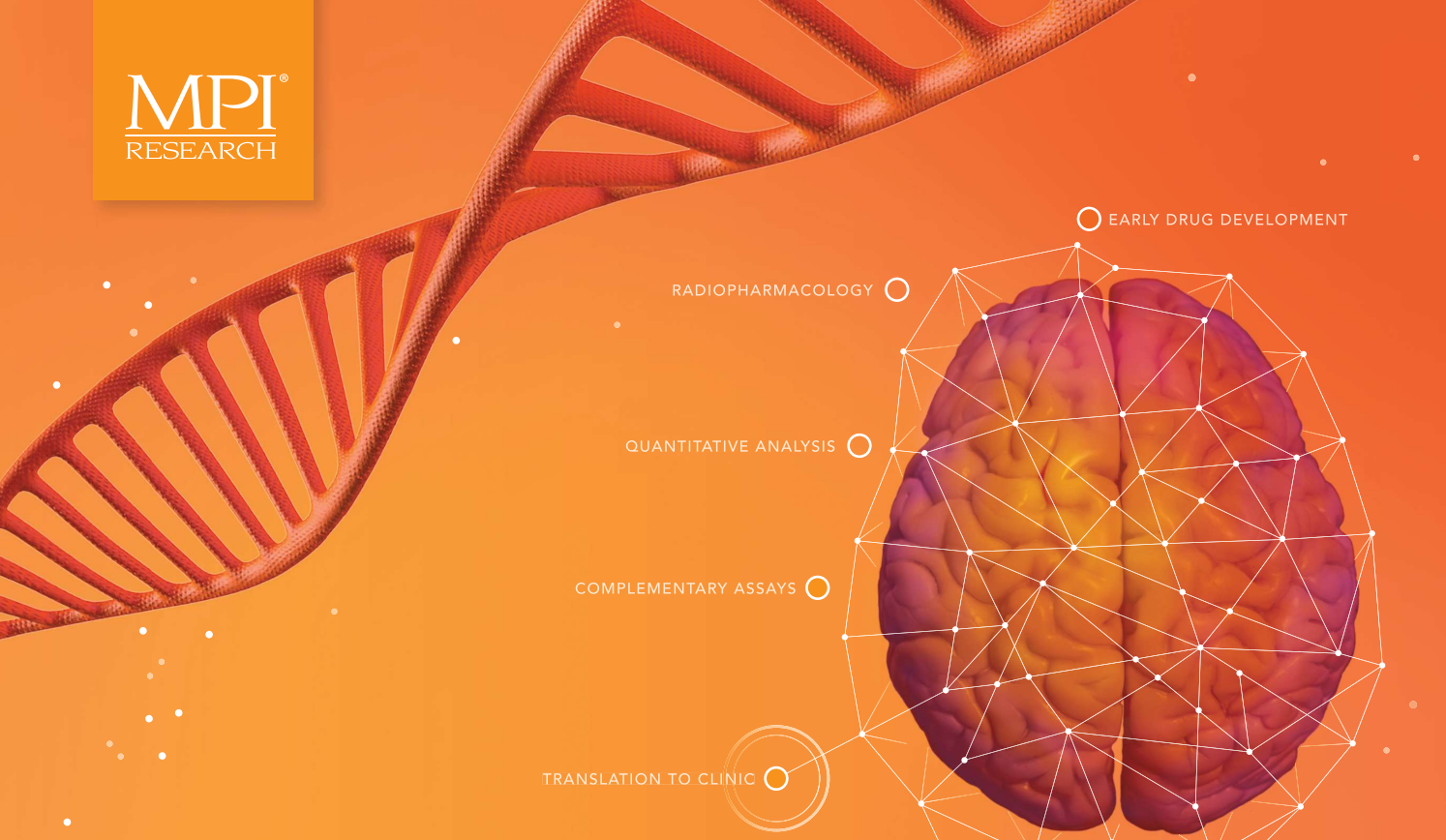

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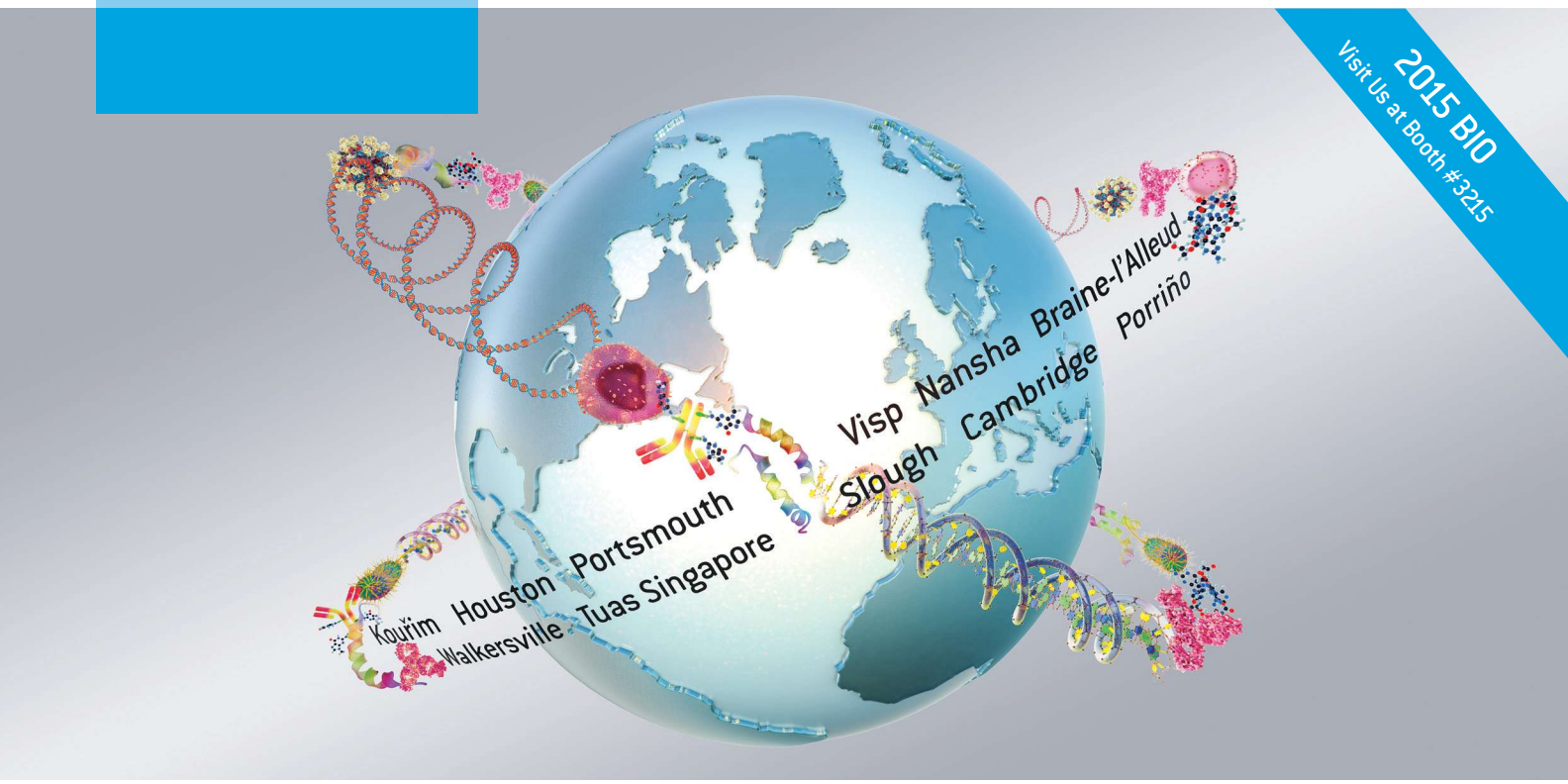

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Does Your Company Have a Quality Culture?

ROB WRIGHT Chief Editor

If you have worked at your company for longer than six months, then you can probably describe your organization's culture in one word, which hopefully doesn't involve an expletive. As you can probably attest, depending upon the quality of a company's culture (i.e., high versus low), working there can be either a blessing or a curse. Interestingly, even during these times of uncertainty and high unemployment, approximately two million Americans voluntarily leave their jobs every month. Of the reasons given, leaving a crappy corporate culture behind is among the top five. Although some of you may be thinking "good riddance to bad rubbish" when an employee opts to move on, *Life Science Leader* editorial advisory board member and leadership expert, Mike Myatt, reminds us that few things in business are as costly and disruptive as an unexpected departure, especially when it is of the top-talent variety. According to Myatt, employees who are challenged, engaged, valued, and rewarded (emotionally, intellectually, and financially) rarely leave, and more importantly, they perform at very high levels. In other words, creating a culture of quality not only means greater job satisfaction, greater productivity, and less turnover, but it also implies fewer mistakes — a pretty important concept when it comes to the manufacture and distribution of safe and efficacious medicines.

At a recent ISPE (International Society for Pharmaceutical Engineering) Quality Metrics Summit, it was evident that today's bio and pharmaceutical drug manufacturers focus on providing a safe, compliant, and reliable supply. But it was clear that creating a culture of quality, not just at one's own organization but throughout our entire biopharmaceutical manufacturing industry, plays a pivotal role in this process. During the opening plenary session, Willie Deese, EVP and president of Merck's manufacturing division, stated that at his organization, the focus is on measuring supply chain performance using metrics that are predictive of outcomes. "Our pursuit is to be good, not to look good," he said. "In the process of being good, you will in fact, look good." For Deese, the key is not just measures and metrics but consistent leadership enabling a culture of accountability that is connected to the customer, so everyone understands why the work they do is so important. "People often ask, 'Can you measure culture?'" he stated. "I would say it's a difficult thing to measure. But it's not difficult to determine whether or not you have the right culture."

This month's cover story (p. 20) features Bruce Cozadd, Jazz Pharmaceuticals' cofounder, chairman, and CEO. Unlike most start-ups where founders first focus on products, leaving the corporate culture to evolve on its own, Cozadd and his cofounders concentrated on creating a company – culture first. He said if you have been in or around a strong positive corporate culture, you realize the benefits it provides in getting a company through the tough times (e.g., when Jazz was trading for < $1 a share). Unfortunately, if a company's culture is not what you want, Cozadd believes it can be very hard to change, even from the CEO seat. Having gone through two pharmaceutical industry company culture change initiatives (e.g., Mead Johnson Nutritionals and Organon Biopharmaceuticals), I concur with his assessment. If you want high-quality people, products, and eventually profits, consider Cozadd's approach, which began with not just building a high-quality corporate culture but measuring it as well. L

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Q What are some best business practices for selecting a supply chain vendor so as to maintain quality?

A FIRST, LOOK FOR SUPPLIERS THAT UNDERSTAND, RESPECT, AND ACCOMMODATE your internal values and expectations. Such suppliers share a common commitment to behave ethically, with integrity, and compliantly. They incorporate quality, safety, and sustainability into their operations, and they place patients and customers at the center of what they do.

Remember, it's not just about cost; it's about total value. We evaluate suppliers on such things as quality, reliability, innovation, speed to market, business continuity, sustainability, growth, flexibility, and cost. Quality is a more heavily weighted criterion.

Lastly, we perform technical and quality assessments jointly, via cross-functional teams. This helps assure that all business partner concerns are addressed and weighed appropriately, before deciding to engage a new supplier. This also allows the potential identification of technical issues that could develop into future quality problems.

ANU HANS
is the VP and chief procurement officer, enterprise supply chain at Johnson & Johnson. She also serves as a board member for DCAT.

Q What are the regulatory roadblocks ahead for personalized medicine, and how can these be overcome?

A THE INDUSTRY NEEDS GREATER CLARITY on a global basis for the support of codevelopment programs. Although companion diagnostics and their targeted therapies are available in markets outside of the U.S., regulatory bodies outside of the U.S. are woefully behind in providing clear regulatory guidance for codevelopment programs. Newer technologies (e.g., next generation sequencing [NGS]) have gained rapid and broad use in research, clinical investigations, and assignment of drug therapy. However, NGS does not yet have a defined regulatory pathway for approval. A regulatory-approved pathway is needed to ensure accurate test results for patients. Companion diagnostic tests developed by diagnostic manufacturers face higher regulatory hurdles than laboratory developed tests (LDTs). As there has yet to be a regulatory review of LDTs used as a companion diagnostic, manufacturers are disadvantaged and disincentivized thus discouraging innovation.

DR. TIM GARNETT
is the chief medical officer and senior VP of Medicines Development Unit (MDU) for Lilly and is responsible for medical, regulatory, global product safety, and global health outcomes.

Q How does the interpretation of Hippocrates' statement, "Declare the past, diagnose the present, foretell the future" apply to antibiotic development?

A THE GAIN ACT AND THE OBAMA ADMINISTRATION'S executive order are acknowledgements of the need for action to tackle resistance and stimulate development of treatments. FDA efforts have focused on streamlining the antibiotic regulatory pathway, yet there is a need for more guidance on how to convey a drug's possible effectiveness against resistant pathogens on the label. In the absence of rapid diagnostics, physicians receive causative pathogen and susceptibility information *after* a patient has started therapy. The antibiotic label is the best source for useful information about performance of an antibiotic in the context of resistance patterns. It is imperative to juxtapose what we know from the past – that is – how the antibiotic has performed against known mechanisms both *in vitro* and in the clinic – with what is unknown because the only certainty is that pathogens will adapt and evolve.

BARRY EISENSTEIN, MD, FACP, FIDSA, FAAM
is senior VP of scientific affairs at Cubist Pharmaceuticals.

Opioid Epidemic Draws Congressional Scrutiny

JOHN McMANUS The McManus Group

The opioid abuse epidemic, which started in the South and Appalachia, has spread nationwide and is now receiving heightened attention from policymakers. Opioids, which have been used for hundreds of years to relieve pain, have addictive properties with high risk for abuse and are often connected with unintentional overdose and polypharmacy with the elderly. More than 16,000 people die in the U.S. each year from overdoses of pain relievers — more deaths than any other drug, according to the Pew Charitable Trusts.

Policymakers are grappling with balancing two competing goals of restricting clearly abusive consumption of opioids by many addicts with appropriate access for patients who truly need them to treat severe and chronic pain.

In addition, consumption of "synthetic" opioids — drugs meant to deter overdoses or utilization of methadone restricted to a clinic setting — has been a deliberate public policy since enactment of the Drug Addiction Treatment Act 15 years ago.

According to the Substance Abuse and Mental Health Services Administration (SAMHSA), which is tasked with leading the country's public health response to opioid and heroin addiction, nearly 1.5 million addicts were "treated" with synthetic opioids in 2012 — a five-fold increase in the last 10 years. At a recent Energy&Commerce Committee Oversight and Investigations Subcommittee hearing, Chairman Tim Murphy (R-PA) said, "I do not call this 'treatment.' It is addiction maintenance."

Even the Medicare program is experiencing the opioid phenomenon. A recent Medicare Payment Advisory Committee's examination of the issue found more than one-third of Medicare beneficiaries — 12.3 million — filled at least one opioid prescription. The top 500,000 Medicare opioid utilizers filled at least 23 prescriptions and accounted for 70 percent of the total $1.9 billion spent on opioids in Medicare in 2012. Almost two-thirds of the Medicare beneficiaries who utilized opioids qualified through their disability status.

Opioid addiction can have tragic clinical and human consequences, especially with pregnant addicts, as newborn babies become addicted while in the womb. Newborns exposed to opioids in utero may be born prematurely with low birth weight, have feeding difficulties, irritability, and seizures, and experience significantly longer hospital stays. Withdrawal symptoms, referred to as "neonatal abstinence syndrome," develop shortly after birth. Symptoms include loud, high-pitched crying, sweating, tremors, and gastrointestinal and respiratory difficulties.

A February 2015 Government Accountability Office (GAO) report on prenatal drug use and newborn health found that the government needs a better coordinated approach to this growing problem. The GAO commented that within Health and Human Services, there are nine agencies that address prenatal opioid use, but HHS "lacks a focal point to lead planning and coordination of efforts related specifically to opioid use or neonatal abstinence syndrome across the department ... which limits the effectiveness of federal efforts to reduce prenatal opioid use among pregnant women. Additionally, there is a risk that federal efforts may be duplicated, overlapping, or fragmented."

"A recent Medicare Payment Advisory Committee's examination of the issue found more than one-third of Medicare beneficiaries — 12.3 million — filled at least one opioid prescription."

Local leaders at the front line of the epidemic are not waiting for the federal bureaucracy to coordinate a plan. Dr. Stefan Maxwell, of the MEDNAX Medical

Group and chair of the West Virginia Perinatal Partnership, commented, "Pregnancy offers a unique opportunity for treating substance abuse because women are typically highly motivated to modify their behavior and deliver a healthy baby." In 2012 the Partnership embarked on a Drug Free Moms and Kids project to provide a comprehensive effort to screen all women in eight hospitals at their first pregnancy to identify those who use drugs and provide treatment to wean them off drugs. Preliminary results are promising — in one pilot site, those testing positive dropped from 19 percent to 8 percent in the first two years.

Congress is now focusing on the issue. The Energy and Commerce Committee has held a series of hearings to examine the problem and develop solutions. While consensus has not yet been achieved with stakeholders, legislation is now being advanced to address the problem.

Patients addicted to painkillers often get numerous physicians to surreptitiously prescribe opioids, making it difficult for a physician to know whether the patient is taking too much pain medication. The Ways and Means Committee included a provision in its fraud and abuse bill that would have replicated in Medicare the drug management protocols already under way in many state Medicaid programs, which require the patient to receive opioids from only one doctor and fill them at a single pharmacy.

While that provision was dropped from the landmark Medicare Access and CHIP Reauthorization Act that repealed the Medicare sustainable growth formula, the Energy & Commerce Committee has picked up the concept in its 21st Century Cures legislation, a bill that represents more than a year's worth of work by the Committee. But rather than restrict the patient to a single physician prescriber, the Energy and Commerce Committee bill would restrict the patient to a single pharmacy.

As might be expected, the single prescriber proposal has faced opposition from the American Medical Association and other physician groups, and the single pharmacy provision has generated opposition from some pharmacy groups, including the National Community Pharmacists Association.

A more fundamental problem is that the solutions themselves often beget different, more serious problems. For example, the National Association of Pharmacy Board's InterConnect program facilitates the transfer of prescription monitoring program (PMP) data across state lines to authorized users, and 28 states are now participating. It allows participating state PMPs across the United States to be linked, providing a more effective means of combating drug diversion and drug abuse nationwide. This has made abusing prescription opioids more difficult.

However, this program, as well as a reformulation of OxyCotin to make it harder to abuse, may have caused heroin use to spike dramatically. Theodore Cicero, a psychiatry professor at Washington University said, "Much of the heroin use you're seeing now is due in large part to making prescription opioids a lot less accessible." The increased use of heroin and other opioids has also facilitated new outbreaks of HIV and Hepatitis C infections among this population, as addicts share dirty needles.

The Centers for Disease Control reported that a "severe outbreak" of HIV infections has soared in rural Indiana among users of a prescription opioid called Opana, which must be injected multiple times a day. More than 142 people were infected in Scott and Jackson counties, which have a population of only several thousand people, prompting the state to declare a state of emergency for that area. Conservative Governor Mike Pence (R-IN) also signed an executive order providing needle exchanges, which studies show reduce new infections.

Similarly, the Affordable Care Act, which requires Medicare patient satisfaction surveys to help rank hospitals in the Value-Based Purchasing program, could be contributing to prescription opioid drug abuse phenomena. In 2014, Senators Chuck Grassley (R-IA) and Dianne Feinstein (D-CA) wrote to the Centers for Medicare and Medicaid Services (CMS) "There is growing anecdotal evidence that these surveys may be having the unintended effect of encouraging practitioners to prescribe [opioid pain relievers] unnecessarily and improperly," in order to solicit higher patient satisfaction surveys. Anna Lembke, MD, a professor of Psychiatry at Stanford University, testified at Energy and Commerce, "Many doctors are afraid that patients will sue them or complain about them if they don't prescribe opioids, even when the doctor knows the opioid is harming the patient ... Congress can push back against the opioid epidemic by requiring a revision of heath care quality measures to reduce over-prescribing."

Obviously, no single solution will solve this complex problem. Multi-pronged approaches that are being tested in communities should be examined for propagation across the country. This will require bringing all stakeholders to the table and constantly monitoring what works and what may be producing unfortunate side effects. L

JOHN MCMANUS is president and founder of The McManus Group, a consulting firm specializing in strategic policy and political counsel and advocacy for healthcare clients with issues before Congress and the administration. Prior to founding his firm, McManus served Chairman Bill Thomas as the staff director of the Ways and Means Health Subcommittee, where he led the policy development, negotiations, and drafting of the Medicare Prescription Drug, Improvement and Modernization Act of 2003. Before working for Chairman Thomas, McManus worked for Eli Lilly & Company as a senior associate and for the Maryland House of Delegates as a research analyst. He earned his Master of Public Policy from Duke University and Bachelor of Arts from Washington and Lee University.

Genkyotex

Inhibiting NOX enzymes back to normal levels may forestall the ravages of reactive oxygen species in multiple diseases.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Genkyotex has discovered and is developing a range of compounds to inhibit a family of enzymes called NADPH (nicotinamide adenine dinucleotide phosphate) oxidases, or NOX, which when elevated above normal levels, have pathological effects in a host of disease areas, including diabetes, kidney disease, cardiovascular, CNS, and various fibrotic and inflammatory conditions. Its lead compound has just completed a Phase 2 trial in diabetic nephropathy.

WHAT'S AT STAKE

Oxygen, like fire, has two faces, one life-giving, the other destructive — breath or rust. And so it is with the multitude of molecular species of oxygen coursing through our bodies along physiological pathways. A small fire lends warmth; a large one, raging out of control, wreaks pain and even death. Genkyotex turns that metaphor toward a constructive purpose; the company founders built upon the discovery of NOX enzymes in the early 2000s by elucidating seven different NOX isoforms and eventually launching drug development programs among the first five, which all play a positive role in our health at normal levels but aggravate a variety of disease states when overexpressed. Essentially, the scientist-founders searched for and discovered NOX inhibitors that return expression to normal levels.

"NOX enzymes produce superoxide and other down-stream reactive oxygen species [ROS], which normally have a basal physiological role, but under certain conditions the enzymes cause overproduction of ROS, leading to major pathological effects," explains the company's CEO, Ursula Ney. "Overexpressed ROS can cause the oxidization of proteins, including DNA, and have a negative effect on multiple signaling pathways. Our NOX inhibitors interrupt and modulate ROS overexpression and thus the pathological mechanisms."

In some cases, Ney says, more than one NOX enzyme is involved in the pathology of a disease. "We have a unique assay platform that allows us to screen against each of those enzymes for activity, which means we can design molecules with the right profile of NOX inhibition to target a particular disease." Genkyotex's lead compound, GKT137831, now having completed a Phase 2 trial in diabetic nephropathy, inhibits NOX 1 and 4. A readout of the trial results is due about the time this column goes to press.

The range of diseases potentially amenable to NOX inhibition is really quite remarkable. The company is also investigating GKT137831 and another NOX 1/4 inhibitor, GKT901, for treating various fibrotic and inflammatory conditions, and its early stage pipeline includes a NOX 1 inhibitor targeting atherosclerosis and other vascular conditions, colon disease, and Parkinson's, as well as a NOX 2 inhibitor versus CNS conditions.

"NOX 4 is important in the fibrotic process," Ney says. "NOX 1 and NOX 4 are also important in the associated inflammatory process, which amplifies the fibrosis, regardless of the organ. We have data in liver fibrosis, including NASH [nonalcoholic steatohepatitis], and in lung fibrosis. So with our lead molecules, we have a really strong opportunity in a broad range of indications in fibrotic diseases." Safety has not been an issue up to this point. As with other inhibitory drugs, such as anti-TNF, the Genkyotex compounds appear to return the targets to normal levels rather than below them.

Besides pursuing the lead indications, the company's strategy includes broadening applications for its NOX 1 and 4 inhibitors as well as determining potential indications for inhibitors of the other NOX isoforms. As it looks for industry partners and contemplates a public listing, Genkyotex continues to receive significant support from an impressive array of investors and non-equity funders. Research partners include the Neurinox consortium, drawing on €1.2 million in funding from the European Community to study the role of NOX enzymes in neurodegenerative disease, particularly amyotrophic lateral sclerosis (ALS), and the Juvenile Diabetes Research Foundation (JDRF) in the United States, to subsidize work in diabetic nephropathy.

URSULA NEY, PH.D.
CEO

Vital Statistics

21
Employees

Headquarters
Geneva, Switzerland

Finances

Total raised
$76.3M

Seed: **$0.9M**

Series A: **$1.4M**

Series B: **$6.6M**

Series C: **$20.4M**

Series C extension: **$26M**

Series D: **$21M**

Investors: Eclosion, Edmond de Rothschild Venture Capital, Vesalius Biocapital Partners, Neomed Management, BioMedInvest, VI Partners, MP Healthcare Venture Management, Société Générale Asset Management (SGAM SEFTI).

Research partnership funding

Total funding
$4M

Neurinox consortium, Juvenile Diabetes Research Foundation (JDRF).

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Biomarkets: Looking For The Hole In The Donut

ALLAN L. SHAW

"While the scientific risks are daunting, the commercial risks may prove to be the biggest long-term challenge."

The capital market IPO drought of 2008 to 2012 seems like a distant memory — funny how more than 120 IPOs can make us forget such a painful period. Furthermore, the strength of the biopharma sector has been buoyed by the stellar performance of large cap stocks driven by exciting product launches and impressive clinical data. Not since 2000 has the industry experienced such relevance and broadened interest, as evidenced by the investor cash inflows. Given this incredible run, the market has become increasingly optimistic, at times even displaying a cavalier disregard for the risks and execution challenges implicit within the biopharma industry. While such success has left most industry stakeholders pinching themselves, for many it has also called into question the valuation levels we see today. Is this run-up in sector valuations an indication that we are in the midst of a bubble?

Remember, though, the market is still exhibiting elements of rational behavior. For example, during the last two years, nearly a third of the biopharma IPOs have traded below their initial offering price.

Nevertheless, there is certainly reason for bubble conversations to be taking place. The big question is: How did we get here, and where are we going? This euphoric period for biopharmaceuticals, notwithstanding high valuations by all conventional metrics, has been driven by a confluence of fundamental dynamics such as:

- low interest rates (desire for beta [i.e., the tendency of a security's returns to respond to swings in the market])
- lack of risk-capital alternatives (e.g., funds used for high-risk, high-reward investments such as emerging markets, precious metals, or emerging biotechnology stocks)
- generalists' (vs. industry specialists) capital allocation to biopharmaceuticals
- FDA lowering the bar (i.e., record new drug approvals, particularly with biologics)
- capital/clinical efficiency and proliferation of targeted therapies, orphan diseases, new modalities and technologies (e.g., gene therapies), and new drug categories (immuno-oncology) reflecting better scientific understanding of the mechanism of diseases coupled with our evolving knowledge and application of genomics coupled with companion diagnostics
- increase in specialty-drug spending related to new and exciting drugs launches (e.g., Solvadi, Keytruda, Yervoy/Opdivo, Tecfidera)
- the shift in Big Pharma resource allocation has created a proliferation of M&A and partnering deals, which indicate a de-emphasis on internal research and increased emphasis on external collaborations
- the emergence of a supply/demand imbalance for new companies (The capital markets' prior drought adversely impacted the VC community and its capacity to create new companies. This lack of startups or eco-system deficiency has given rise to demand-driven premiums for innovative drugs and technology platforms.)

These market drivers reflect an industry that is maturing and is no longer considered a backwater asset class for investors. Just look at the proportional growth of biologics prescriptions relative to total scripts, clinical success/efficiency (e.g., three-fold increase in productivity of blockbuster agents since 2010[1]), and the dramatic rise in new drug approvals (hitting an 18-year high in 2014, with biologics representing 35 percent of new drugs approved[2]).

These factors all have contributed to the

significant increase in capital allocation as evidenced by the huge fund inflows to biologics.

BIOPHARMA INDUSTRY RISKS

All of these changes have led investors to conclude that an industrial paradigm shift is afoot, which, in turn, has caused the market to rationalize valuations and ignore the inherent industry and macroeconomic risks, such as:

- pricing headwinds and cost-containment initiatives
- clinical attrition
- regulatory hurdles
- safety risks
- competitive landscape
- reimbursement challenges
- rise of biosimilars
- intellectual property challenges
- unfunded business plans (Many developmental-stage companies generally have enough financial resources to only achieve valuation inflection points — hopefully — that correlate to clinical/developmental activities, reflecting their dependency on evergreen access to capital markets.)
- execution risk
- interest-rate hikes.

The biopharmaceutical sector is the epitome of risk (e.g., scientific, clinical, regulatory, commercial). These industrial jeopardies are pervasive and represent significant operational and strategic challenges that may not be fully appreciated nor adequately represented in company valuations. This begs the question, "What happens when the capital markets reacquaint themselves with risk?" Despite the significant advancements in efficiency and effectiveness previously referenced, only a relatively low percentage of clinical-stage products under development will be successfully commercialized. This leads us to question whether or not those inevitable outcomes are reflected in the capital markets (i.e., can everyone be a winner?). This point is particularly acute when considering the emerging innovative medicines/technologies that are in development (e.g. CAR-T [chimeric antigen receptors T-cells], gene and immunotherapies) because they take longer to develop/commercialize and their limited patient experience/history implicitly means higher risks. A good example is RNAi (ribonucleic acid interference). RNAi initially suffered because development took longer

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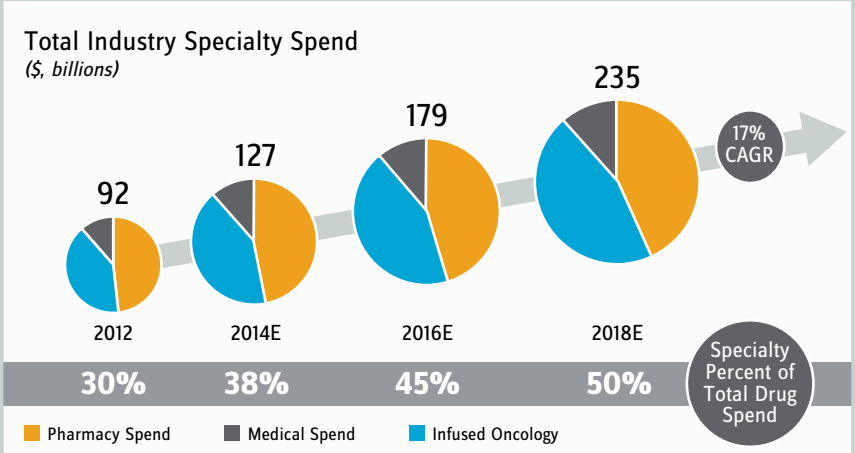

Source: NHE, Artemetrix, CVS/caremark internal analysis, 2013.

than anticipated, but now it is starting to show immense potential more than a decade after its debut. This underscores the point that good science coupled with time and money can overcome obstacles, but success can require significantly more resources, perseverance, and luck than originally anticipated. Clearly, the business of drug development is not for the faint of heart.

PRICE/COST CONTAINMENT ISSUES

While the scientific risks are daunting, the commercial risks may prove to be the biggest long-term challenge. Consider the global cost-containment initiatives aimed at tethering unsustainable healthcare spending. These initiatives have created concerns that the healthcare system will not be able to support widespread access to beneficial medicines. Although drugs represent a relatively small proportion of total healthcare costs, they are still destined to come down in price as outcomes-based/capitated pricing (dare I say, "risk-sharing" or "value-based pricing"?) that emphasizes cost-effectiveness becomes the norm.

Europe (e.g., U.K. and Germany) offers insights into cost-containment models that have effectively created downward pricing pressures on drug manufacturers. The U.K.'s NICE (National Institute for Health and Care Excellence) could provide foresight of things to come. Currently, the price of a drug in the U.S. is often twice or possibly even five times that of the same drug in Europe. This begs the question: "How long will the U.S. continue to subsidize global medicine?"

Unfortunately, only through hindsight will we be able to answer any of the questions we've posed here regarding the industry's valuations/expectations and related risks. I am not sure we could ever agree where we go from here, but nevertheless, I would suggest the following:

- Do not try to time the market; grab the money when you can.
- Go public when you can; companies have much better success with capital market access once they have listed their securities.
- Continue allocating resources in the same manner you did with your last $100. Organizations are generally more effective with capital deployment when they have less as opposed to more.
- Make sure your business plans are funded to the next value inflection point along with some additional reserves in case things do not evolve as planned.
- Focus on keeping your promises to maintain creditability with investors and market access. Maintain investor confidence; access to the capital markets is a privilege and not an entitlement. Embrace the fundamental principle of under promising and over delivering.
- Apply the lessons learned from the last capital market drought. Did you learn any?

Moving forward, we can be certain there will be more big winners, but it is important to understand there will also be losers. Perhaps the capital markets are behaving rationally on a macro level and will simply be reallocated among winners and losers with outsized gains/losses — rewarding companies that are executing and penalizing those that are not. In a rising tide, all boats are lifted; it is when things get tough that the true mettle of management teams is tested. As such, pick your management teams wisely. If history is any indication of the future, trips to the capital markets will not continue to be as easy as visiting your ATM machine — though only time will tell. L

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CRO Or CMO: Which Is Best For Your Preformulation Needs?

The quality of a drug's final formulation depends on (among other things) the quality of the studies completed in the preformulation stage. Thus, careful selection of outsourcing partners for preformulation work is crucial, but it's also challenging.

NIGEL WALKER
Managing Director
at That's Nice

> *"As cost pressures have increased in recent years, the level of outsourcing across and beyond the drug development cycle has grown."*

The preformulation stage of drug development is an intermediate stage between the efforts to identify novel new drug substances and the efforts focused on developing a safe and effective drug product. As such, the information obtained in this stage plays an important role in determining whether or not a drug candidate becomes a commercial medicine, which occurs for only a very small percentage of lead compounds.

MANY OUTSOURCING CHOICES

As cost pressures have increased in recent years, the level of outsourcing across and beyond the drug development cycle has grown. As a result, more pharmaceutical companies are outsourcing preformulation studies with the intention of determining the candidates with real potential as early in the process as possible and getting those with the greatest likelihood of success into clinical trials all the sooner. These companies can choose among three types of providers: CROs that focus on discovery services, CMOs that emphasize manufacturing at a larger scale, and CDMOs that offer the full range of services from discovery to commercial production.

Many CROs may have greater expertise in molecule characterization but typically lack familiarity with both final drug products and their dosage forms and the commercialization process. In addition, there will be additional costs associated with selecting a manufacturer and potential risks with technology transfer and scale-up. On the other hand, CMOs that offer preformulation services still tend to have a greater focus on commercialization and may move too quickly to formulation and clinical trial studies. CDMOs theoretically offer the advantages of both — expertise in both investigative techniques and commercialization — and thus should provide the right balance that maximizes the speed of development and reduces overall costs while maintaining the highest level of quality and regulatory compliance.

The choice of a CRO, CMO, or CDMO thus depends largely on the preferences of the pharmaceutical company and its comfort level with other aspects of the drug development process, such as technology transfer and scale-up. A manufacturer that has strong expertise in commercialization or a pre-existing strategic relationship with a CMO that is focused on these aspects of the process may prefer a CRO. On the other hand,

a company that is looking to support its own preformulation expertise but lacks capabilities in technology transfer and scale-up may prefer to outsource to a CMO. Virtual companies that rely completely on outsourcing partners, and pharmaceutical companies that are looking to reduce the number of service providers they work with, may find a CDMO very attractive.

Important points to keep in mind when choosing an outsourcing partner are the potential difficulties and cost associated with switching to another provider. For instance, in some cases, and particularly for biologic APIs and drug products, nonclinicial and clinical study data may no longer be valid; or at the very least, bridging studies may be required. Therefore, regardless of the type of partner, conducting a careful evaluation is necessary to ensure that the right one is selected the first time.

MORE THAN ONE RIGHT ANSWER

A look at the types of service providers that pharmaceutical and biotechnology companies currently outsource preformulation studies to clearly reveals that no one particular type of organization is preferred. Table 1 lists twelve companies that were frequently selected by respondents to Nice Insight's 2015 pharmaceutical and biotechnology outsourcing survey as firms they would consider for formulation/preformulation projects.

The list includes CROs, CMOs, and CDMOs and also contract service providers that are business units of major pharma/biotech companies. This result is not surprising, since nearly three-quarters (73 percent) of survey respondents indicated that their companies outsource to both CROs and CMOs, with only 11 percent and 12 percent, respectively, outsourcing just to CROs or CMOs.

Notably, all of the firms preferred by the respondents to the 2015 Nice Insight pharmaceutical and biotechnology outsourcing survey are located in North America or Western Europe. The companies for which the respondents work are also all located in these two regions, with nearly half (47 percent) of pharmaceutical companies and a little over a third (38 percent) of biopharmaceutical manufacturers. Seventy-three percent outsource to both CROs and CMOs.

TABLE 1:
SERVICE PROVIDERS FREQUENTLY CONSIDERED FOR FORMULATION/ PREFORMULATION PROJECTS

Akorn
Aptuit, Inc.
Baxter BioPharma Solutions
Boehringer Ingelheim GmbH
Confab Laboratories Inc.
CPL Limited
Huntingdon Life Sciences
Next Pharma
Novasep, Inc.
Pharmaceutics International Inc (Pii)
Pharmatek Laboratories, Inc.
Siegfried Ltd.

QUALITY RULES

Given the significant impact the preformulation studies can have on drug development with respect to the development of safe and effective product formulations and the reduction of cost and time to market, it is not surprising that quality is considered the top priority when survey respondents consider CROs and CMOs for preformulation projects. In fact, an industry reputation for doing quality work is very influential when a CRO/CMO is being evaluated for a preformulation project. Service providers that have a demonstrated understanding of their customers' requirements and clearly have good communication skills and are transparent with their clients also receive more attention.

Having a track record of success, financial stability, and experience, and being able to adapt to changing project needs and are also important attributes that survey participants consider when choosing a CRO or CMO for preformulation studies. These results are also not surprising given the central role that preformulation studies play in determing success or failure of a drug candidate to become a commercially viable, safe, and effective drug.

When evaluating the performance of CROs and CMOs that survey respondents have used for preformulation studies, quality is once again the most important metric by far. Interestingly, though, other factors that are not ranked by survey participants as being important when selecting a service provider are considered as important performance attributes, including their safety/compliance audit history and cost-effectiveness. Respondents to Nice Insight's 2015 pharmaceutical and biotechnology outsourcing survey also indicated that the ability of CROs and CMOs to communicate and their technical expertise are other factors of importance when evaluating performance on preformulation projects. Finally, according to survey participants, both CROs and CMOs can enhance their service by resolving issues in a timely manner, avoiding unexpected charges, and improving product quality. L

Reference:

2015 Pharmaceutical and Biotechnology Outsourcing Survey, Nice Insight, January 2015

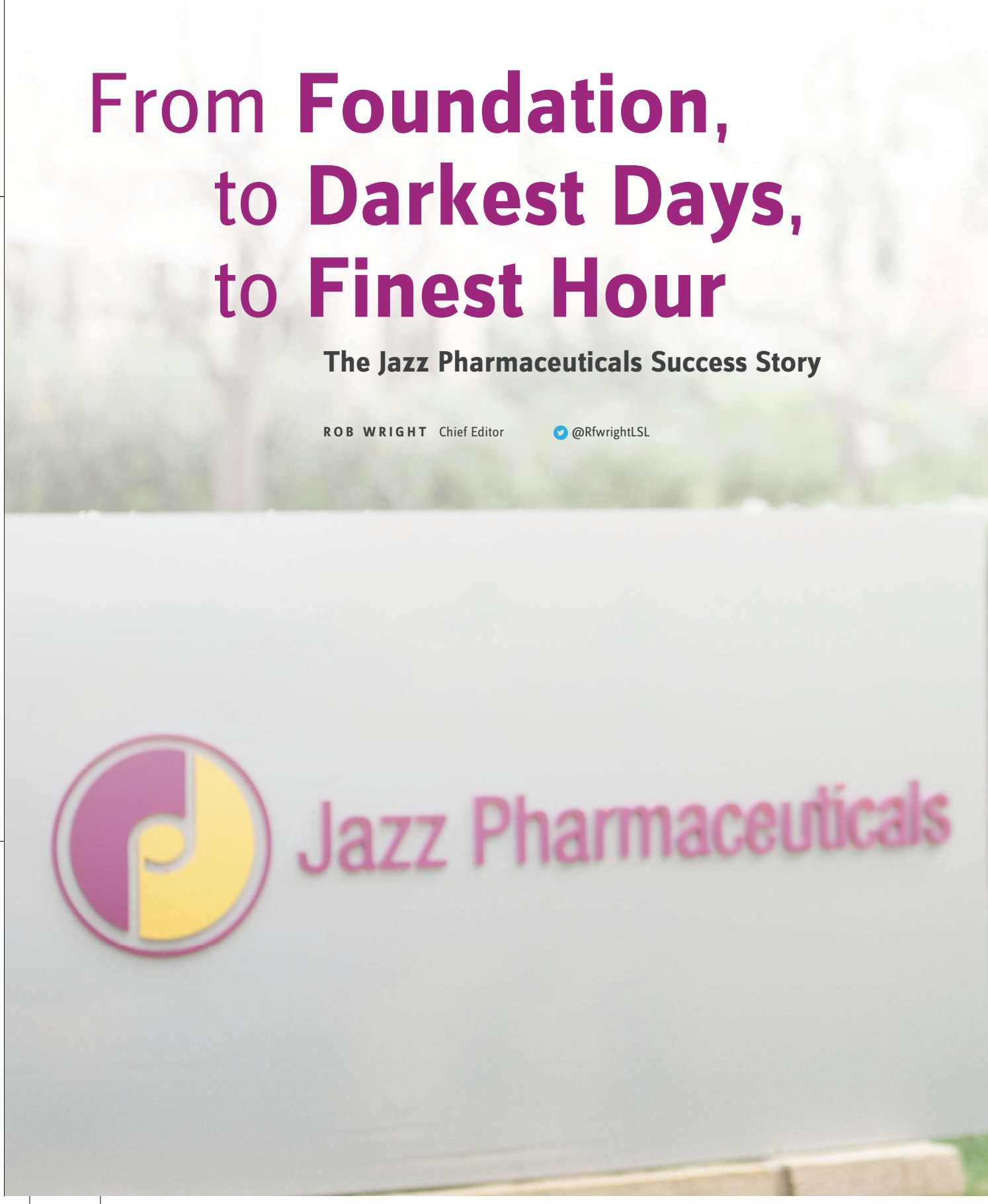
If you want to learn more about the report or how to participate, please contact Nigel Walker, managing director, at That's Nice by sending an email to nigel@thatsnice.com.

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2014-2015 report includes responses from 2,303 participants. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

From Foundation, to Darkest Days, to Finest Hour

The Jazz Pharmaceuticals Success Story

ROB WRIGHT Chief Editor @RfwrightLSL



BRUCE COZADD
Cofounder, Chairman, and CEO
of Jazz Pharmaceuticals

The darkest days of Jazz Pharmaceuticals (NASDAQ: JAZZ) came in April 2009. "Our stock price was 53 cents a share," recalls the company's cofounder, chairman, and CEO, Bruce Cozadd. Having negative equity, $120 million in long-term debt, around $15 million in cash, and being unable to raise capital, Jazz was in serious trouble. "We were in default on our debt, literally talking to bankruptcy attorneys every day," Cozadd says. The decision facing Jazz leadership in December 2008 had been whether to make the next interest payment to debt holders or to fund an ongoing clinical trial. "We had enough money in the bank to make the payment, but we didn't think we had enough to make that payment *and* continue the clinical trial," shares Cozadd. By not making the debt payment, the company was at risk of being shut down. Nevertheless, the leadership of Jazz decided to use the money toward continuing the clinical trial.

Six years later, with a market cap over $11.3 billion, the stock trading over $180 a share, and Jazz being viewed as one of the hottest Big Pharma targets of acquisition, it is easy to say they made the right decision. "Sure, it's a great story *now*. But at the time we didn't know it would work," Cozadd admits.

After such an experience, you would expect him to point to cash flow management as being the critical component of the Jazz success story. But instead, it's the company's culture that he regards as the linchpin, and surprisingly, that emphasis on a strong corporate culture was in the plans from the company's genesis.

Culture First; Products Second

Most companies create their organizational culture well after developing their first product. Cozadd and his cofounders took the opposite approach. In fact, the company did not even have a product or specific R&D program when it was launched in 2003. Sure, Cozadd had some ideas of what the company might want to work on, but his primary focus was to build a team capable of creating a strong corporate culture. That meant choosing partners who were like-minded regarding the value of a corporate culture. And since Cozadd had learned the importance of culture during his time at ALZA Corp. (see sidebar), he reached out to two former colleagues — Sam Saks (immediate past CEO of Jazz Pharmaceuticals) and

> *"We had enough money in the bank to make the payment, but we didn't think we had enough to make that payment* and *continue the clinical trial."*
>
> **BRUCE COZADD**

What Are You Doing To Stay On Top Of Your Company's Culture?

"Is the culture what I say it is?" That's the question Bruce Cozadd, cofounder, chairman, and CEO of Jazz Pharmaceuticals, says you have to keep asking yourself as an executive. Cozadd does two things to try to stay on top of Jazz's corporate culture. "First, I spend a lot of time with new employees," he shares. "I invite new employees in for an hour-long breakfast meeting that is relatively unscripted and includes small, cross-functional groups." He says it's important to meet with new employees specifically because their experience of the company's culture is, by definition, whatever the culture is today. "If I ask a tenured employee to describe the Jazz company culture, they may give me an answer formed by something that happened to them three years ago," he explains. "New employees aren't reflecting back to the past to define your company's culture. What they are telling you is what they think the culture is like today."

The other thing Cozadd does to keep tabs on the Jazz corporate culture is a yearly, all-employee, anonymous survey, which includes questions about culture. The company often gets a 90+ percent participation rate with the survey. Employee comments from last year's survey consisted of 57 pages. "I read every comment," Cozadd says. But conducting a survey and reading comments is just the start of the process. "I'm very transparent about reflecting back to the organization as to what I heard and how it compares to previous years," he attests. Because of employee turnover, Cozadd realizes survey results and comments won't be a perfect match from year to year. However, he feels it is still a good tool to provide you with key trends. "I think being willing to solicit honest feedback in an anonymous forum is also helpful to staying on top of your company's culture."

The Birth Of A Corporate Culture Philosophy

Bruce Cozadd, cofounder, chairman, and CEO of Jazz Pharmaceuticals, says his most important corporate culture education began in 1991 when he was hired by ALZA Corp. The company was founded by Dr. Alejandro Zaffaroni, a Uruguayan-born biochemist credited with starting at least 10 companies in Silicon Valley and mentoring a number of start-up entrepreneurs. "I was inspired by his company vision not only from scientific and technical standpoints but also from a business standpoint," says Cozadd. He describes his 10-year experience at ALZA as being "very formative" to the importance he now places on being purposeful and proactive when it comes to creating and managing a company's culture. "I had nothing to do with shaping the culture at ALZA," Cozadd admits. "The company had been around for decades before I joined, but it was powerful, and it was consistent. To this day, almost 15 years after the end of ALZA, people who were there still talk about the ALZA culture." The end of ALZA came through acquisition by J&J for $10.5 billion in 2001.

After taking some time off to focus on his wife's career and spend time with his young children, Cozadd began looking to get back into the biopharmaceutical business. "When I started looking at CEO positions of bioscience companies in the San Francisco Bay Area, I found some businesses that were appealing, but often their corporate cultures were not," he explains. "I had to decide if I wanted to go somewhere and try to change the existing culture, which I viewed as a three-to five-year project, or start a company with a culture that is exactly what I want."

Bob Myers (current president and CEO of Orbus Therapeutics).

The three became the cofounders of Jazz, and then they all quickly reached out to other former ALZA colleagues to join the company's ranks. Cozadd believes this was important because it gave the team instant credibility. "Being an intact, proven team with collective success, not just a group of individuals with individual successes, gave us the ability to go out and raise capital pretty aggressively." (see sidebar)

Two Unusual Challenges

As a new start-up, Jazz Pharmaceuticals needed what every other fledging business needs – capital. In particular, the company was seeking to raise $250 million in its first round, a sum Bruce Cozadd, cofounder, chairman, and CEO of Jazz, says was unheard of at the time. But the amount of money it wanted wasn't the only problem; it was how it wanted to spend it that really became a stumbling block for investors. "We weren't saying give us $250 million and we'll invest it in that product or this R&D program. Instead, we said: 'Give us a pool of money so we can make multiple investments in commercial and R&D products,'" Cozadd explains. The idea was analogous to the company playing the role of an investment fund (i.e., a portfolio approach) and would be better for everyone, including shareholders. "If an R&D program was limping along and the question was, do you kill it or not, it's a lot easier to kill it if it's one of your programs and not your only or most advanced program," Cozadd states. While applying this unbiased approach sounds good in theory, imagine telling investors they were investing in a blind pool with nothing prespecified. "Of course, as members of our board, they were going to get to vote on major expenditures of capital," he relates. "I just couldn't tell them at the outset what we were going to be investing in."

Eventually, the funding came through, but the company faced a second hurdle that actually came from the very thing responsible for helping land those investors – the experienced management team. The value of an intact team and shared experiences may have been beneficial to raising funds, but over the long term it became a liability. "When we ran into a new and serious problem and looked around the management team table for solutions, we were all turning to the same page in the same playbook," Cozadd states. What Jazz didn't have was 10 different people sharing 10 different scenarios from their professional experience. "It's diversity of thought that often gets you to the best answer," he affirms. "With a diverse team to start with, I don't think we could have raised the capital we did. Yet, without diversifying the team over time, I don't think we could have succeeded in the long run."

Creating The Jazz Culture

According to Cozadd, creating a company culture isn't a simple exercise of asking the question, "What kind of culture do you want to have?" and then coming up with a list of principles and values. "It's how you define those values. It's really about how you want to treat people," he says. Therefore, the management team had a daylong meeting to talk about values and what culture was going to mean to them. They discussed terms such as collaboration and what that would mean inside the organization and with external entities such as regulators, payors, and patient advocacy groups. They talked about integrity ("If you make a commitment to somebody either inside or outside the organization, you mean it.") and the importance of transparent communication. Additional meetings were called to discuss how they would recruit people, the specific attributes they were looking for in a candidate, and how they would communicate the company culture throughout the hiring process.

Cozadd likes to say to the Jazz talent acquisition group, "It's not how you treat the top candidate you can't wait to hire, but how you treat the candidates you don't think are a good fit, because they are going to go talk to their friends about their Jazz experience."

Eventually the team identified five core values — integrity, collaboration, passion, pursuit of excellence, and innovation. In addition, the group determined it wanted the organization to be not just a great place to work but also one that puts patients first.

> *"One of the challenges of the biopharmaceutical industry is innovating in a highly regulated environment."*
>
> **BRUCE COZADD**

What's In A Name

It's no accident that Cozadd's company shares its name with a style of music that embraces improvisation but also cohesion. Jazz musicians are mostly known for being great soloists and virtuosos of their instruments. But great jazz musicians must also be able to play well together. That's the kind of corporate culture the company's management team wanted from the beginning. "This concept of individual excellence, but playing well with others, is what I was looking for in a management team," Cozadd says. As for improvisation, he says in the business world that equates to innovation. "One of the challenges of the biopharmaceutical industry is innovating in a highly

regulated environment," he states. "There are things you can play around with, and there are things you can't – just like in jazz music."

Today, the importance of company culture permeates Jazz from the onboarding process and employees' performance reviews to recognition and promotions. "During your performance review, don't tell me how well you did in meeting the objectives of your job, tell me *how* you met those objectives," Cozadd says. "Did you run over everybody and leave bodies in your wake? If so, that's not the culture we want – even if you did meet your goals."

Cozadd believes the key to creating a culture like Jazz's is to provide an environment of meaningful work where people are doing what they are passionate about in a place they are proud to be a part of. And so far, that philosophy seems to be working out. L

Does Your Culture Build Loyalty?

Jazz Pharmaceuticals, like many companies during the economic meltdown of 2008-2009, was unable to raise capital and had to cut expenses to stay alive. "We downsized by about 50 percent," says Bruce Cozadd, cofounder, chairman, and CEO. "First, we informed each employee individually. But then I sent an email to the whole company explaining what we were doing and why. Further, I informed everyone we would be having a meeting the next morning, inviting even those people who had just been let go to attend." During the meeting Cozadd didn't mince words for the mixed audience; he was transparent. "I said, 'Look around the room. The people you thought of as valuable colleagues yesterday, part of your team and the fabric of this company, did not suddenly get less talented in the last 24 hours. This isn't about them. It's about the company's need to survive.'" By having this kind of meeting, Cozadd wanted to minimize the awkwardness between employees that often occurs during a layoff. Eventually, the company did bounce back, and many of those employees were rehired. Cozadd says the fact that these employees chose to come back to work is a clear indicator that Jazz has a strong corporate culture.

"It is not how you treat your star performer whom you're promoting but how you treat the employees you have to let go. What are they going to say about the company after they walk out the door?" Cozadd says.

LEADING DIVERSITY & DISCOVERY AT JANSSEN | By W. Koberstein

ANUK DAS
head of the Disease Integrative Biology, Immunology Research unit at Janssen R&D

Leading Diversity & Discovery At Janssen

Anuk Das Champions Multicultural Networking In Immunology Research

WAYNE KOBERSTEIN Executive Editor
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Diversity is not just a liberal ideal — it is a portal to discovery. To understand that statement in the context of the biopharmaceutical industry, the words at either end of the sentence must be taken at their largest meaning. Diversity of people and research resources leads to more productive discovery of human potential and new therapeutic entities. Diversity and discovery go hand in hand at Janssen Research & Development, where Anuk Das heads the Disease Integrative Biology, Immunology Research unit, and where she has helped make diversity a cultural priority at the company. (Janssen R&D is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.)

Of course, diversity includes people with a variety of backgrounds beyond the traditional preponderance of Caucasian males "at the top" and, for that matter, right down to the bottom of companies in the past. More females, more people of other ethnic groups and nationalities, and a generally freer mix reflecting the planet's population are all first principles from which diversity in a greater sense grows. (See "Diversifying Leadership Teams With People Who Have The X-Factor" in our April 2015 issue.)

As it turns out, the mentality of inclusion offers other benefits when so much of the innovation involving large companies begins outside of those companies, amongst the amalgam of academics and mostly small enterprises loosely called biotech. Das has built a research network of players in that sector, as well as an internal team to integrate the external network with the company, based on a philosophy of opening doors to a wider mix of people and external research partners. And with significant evidence of

positive results, she believes the new R&D operating model, aligned with the idea of diversity in discovery, may succeed where others have failed.

Das presents us with a case of theory turned to action. In parallel with her leadership of an immunology discovery team and collaborator network, she has championed diversity in employment in the scientific and engineering areas of the company through outreach to students pursuing education and careers in the STEM (science, technology, engineering, and math) fields — leading the creation of a postdoctoral program with the University of Michigan for underrepresented minorities that, Das says, "provides us with opportunities for access to innovative science and a diverse talent pipeline."

A conversation with Das supplies some key insights into several areas at once: the evolution of discovery strategy and structure in a leading, though atypical, Big Pharma company; the ever greater understanding and alignment of drug mechanisms with disease mechanisms; and the overriding value of maximizing the variety of people, disciplines, and research nodes in a largely external discovery network.

Leader Origins

How And Why Did You Join This Industry And This Company?

DAS: Prior to joining the pharmaceutical industry, I was a postdoc in academia in the United Kingdom with a pharmacology background. I joined J&J's pharmaceutical company Centocor in 2001, in the discovery group then called the Immunobiology department, moving there from my first pharmaceutical job, at DuPont Pharmaceuticals, which was also in the United States. In my postdoctoral years, I had done a sabbatical at a large pharmaceutical company, which opened my eyes to the impact pharmacologists in that setting can have on patients with disease. My basic reason for wanting to do pharmacology was to learn how drugs affect biological processes, and I realized that in the pharma world, I would have far more opportunities to apply that knowledge than in academia.

What Were The Major Steps That Led To Your Current Work?

For the first few years, I built up my experience in large molecule drug discovery. I was recruited for my research background in lung inflammation with respiratory diseases, and during my tenure in the discovery group, I essentially laid our foundation for respiratory disease research and progressed respiratory drugs into clinical trials. I also expanded our research and established a new area, in fibrotic diseases, building a portfolio for that as well. Then I was asked to take a role with a new function in Janssen R&D and the Immunology Therapeutic Area called "clinical external innovation," where we would invest in emerging areas of science. We have a commitment as a company to invest with a long-term view, because we believe investing in new areas of science will put us at the forefront of science and pay dividends as we build our external network of collaborators, expand our knowledge of the science, and strengthen our credibility by visibly applying that science to drug discovery.

How Does Your Group Fit Into The Larger Janssen R&D/J&J And Corporate Organizations, Both As A Team And As A Contributor To Drug Discovery?

Within J&J, we have separate divisions for consumer medicines, medical devices, diagnostics, and Janssen [pharmaceuticals]. And within Janssen, there are five therapeutic areas, the Immunology Therapeutic Area being one of them. My group resides within Research Immunology, and the diseases we focus on are priority disease areas within the Immunology Therapeutic Area. Through interrogation of disease data in our Network Pharmacology platform, we have quickly come to a point of validating our hypotheses and predictions derived from the platform. Novel gene connections predicted by the network have been validated, and small molecule targets have been identified. This is a new paradigm for discovering our next generation of therapeutic mechanisms and targets. In drug discovery, it's all about impacting the disease biology with the correct therapeutic mechanism.

These Days, Mechanistic Drug Discovery Is Easy To Take For Granted, But In The Early 1990s, Paul Janssen Told Me He Thought Detailed Understanding Of Drug Mechanisms Lay Far In The Future.

It is so exciting that you bring that up, because my current role is focused precisely on making that happen. In the Immunology Therapeutic Area, we are now at a stage to make disease understanding a reality; and to understand how our drugs are working we also need to learn, in parallel, from examples of patients who have been treated with the drugs. In a large number of clinical trials we've conducted in immunology, together with trials in a range of immune-mediated diseases, we have been forward-looking in collecting samples as well. Those samples are now giving us insights into how the drugs work.

Your Focus Is On Discovery, But It Includes Some Integration With Clinical Development.

We encompass the entire bench-to-bedside-and-back approach in collaboration with other units in R&D. We have taken drugs we discovered at our benches and put them through the clinical trials, and now we are bringing that data back to learn from it and delineate our next generation of therapeutic mechanisms to address disease in new ways. We are focused on novel, differentiated drugs to address the remaining unmet medical needs, so understanding how drugs fail to work is also important.

What Is An Example Of A Particular Disease And Drug Target Your Platform Is Addressing?

For IBD [inflammatory bowel disease], we sought available technologies and potential drug targets where only the gut would have exposure to the drug, thus reducing systemic exposure. Of course, this approach has been used for a very long time in IBS [irritable bowel syndrome], but it is a new concept in IBD. There are quite a few companies pursuing the idea, as well as academic labs. One is the Icahn School of Medicine at Mt. Sinai, with which we have a large collaboration.

Are You The Only Ones Championing The Network Pharmacology Model?

There have been some high-impact journal publications on the model, but nothing has been done at the same scale or with the same strength of data as our platform, which offers a new way and much larger scale methodology for identifying our future targets, with human disease being the key.

Mapping Paths

How Would You Summarize The Essential Steps You Take From Understanding A Disease To More Effectively Targeting Drugs At The Condition?

The key to answering that question is in the name of my group: Disease Integrative Biology. The "disease biology" part is clear: Our mission and our focus is around disease biology. But the "integrative" piece is unique; what it really means is we are studying disease biology through interrogating many different kinds of human-disease data, with the ultimate goal to increase our understanding of the diseases.

There is an overwhelming mass of human-disease data, but we approach it in a unique way by using clinical-network pharmacology modeling platforms — or disease maps — that give us a visual way to interrogate the data in a more thorough and careful manner. The maps also allow us to make connections between different types of genes and interrogate the data in a highly efficient manner.

What Is The Technical Description Of How You Use The Network Pharmacology Platform To Map Disease Biology?

Our Systems Pharmacology and Biomarkers team construct probabilistic graphical models, or "Bayesian networks" — molecular maps for visualizing the molecular pathways in human disease — by integrating transcriptomics (RNAseq or microarray), gene co-expression, and cis-expression quantitative trait locus (eQTL) data. The cis-eQTL data identifies those genes that are most likely to regulate their neighbors in the network, thereby providing directionality to the network links.

The first network we focused on is constructed from molecular profiling data from IBD blood and tissue samples collected from Janssen clinical trials. My team of biologists interrogates the Bayesian network *in silico* — focusing on priority areas of biology important to our IBD disease area. We isolate connected subnetworks relevant to IBD from within the larger networks, identify the subnetworks' key regulators, perform experimental confirmation of the Bayesian network predictions, and prioritize candidate targets to enter the drug-discovery portfolio.

How About A Description Of The Same Process For Laypeople?

Through mathematical modeling using genotype data, our platform can predict how different genes talk to each other or are connected to each other. In the models we use, there is also causality — some genes are regulator genes, with one gene affecting multiple others. We may have a modeled network that shows connections among what we call a "hairball" of 9,000 genes, and we single out areas of the network of importance to us from a biology perspective.

For example, we can ask the question, Is there a biological difference between thousands of samples taken from inflammation sites and sites with no inflammation? And what are the genes associated with those sites, and how are those genes talking to each other? To put it simply, that gets us into the realm of mechanism. So the network is all designed to produce mathematical predictions. Right now, in IBD, we've prioritized some of those genes and see whether the predictions of these genes talking to each other are true. We are testing the predictions *in vitro*, in primary human cell models, to see whether each gene identified as a regulator really knocks down or expresses all the other genes as predicted. We have already gained novel insights into new genes and their association with IBD no one had seen or published before.

What Is The End Goal Of The Network Pharmacology Platform From A Strategic Perspective?

For the past half-decade or so, we have read about how the pharmaceutical industry has not delivered the number of new drugs with the efficacy and safety as expected for the investments made. The majority of our targets in the past — and even in the present — have come from the literature, producing more failures than successes. But network pharmacology gives us a new approach — integrating a mass of human data to identify targets. We first need to invest in this approach to establish its validity, and if it works, we will be in a phenomenally strong position to deliver a sustainable pipeline for immunology.

Diversity — Outside & Inside

At What Point Does "Externalization" Of R&D Come Into Play In Your Group?

My career opportunities certainly broadened my appreciation for leveraging expertise outside of one's own group. For example, we developed our microbiome strategy during my tenure in the innovation unit, and we made it happen by collaborating and seeking external advice. Building relationships with external experts has allowed us to build our internal knowledge of the microbiome area, and we anticipate embarking on additional collaborations. My group is small, and I wanted it to be small, because that forces us to go outside the group to leverage expertise and collaborate with other functions or outside the company to seek expertise anywhere in the world. In the IBD collaboration with Icahn, we will be leveraging our innovation center colleagues, our network of already existing academic collaborators, and perhaps new collaborators as well to help execute on validating our targets. We may even partner at a later point with other companies and experts on discovering new drugs aimed at those targets.

You Have Championed Diversity On Your Team, In The Company, In The Industry. How Does Diversity Impel Innovation?

Innovative ideas for new technologies and medical solutions arise from individuals or groups making connections between two or more supposedly unrelated ideas or existing concepts. That takes diversity in thinking by a diverse group of people working together to find the solution, bringing a wide range of perspectives to the table. Realization of the value of diversity came to me through key personal experiences. First was a diversity program we established jointly with the University of Michigan — a postdoctoral program recruiting minority doctoral and postdoctoral candidates. The power of this program is not only evident in the recruitment of diverse candidates, but also in the richness of the projects developed by the university scientists and our scientists working together in the program.

Then, as I recruited my team for disease-integrated biology, I wanted it to be extremely diverse — not only in the obvious terms of gender, cultural background, countries represented, but also in background and experience. In our group of eight, we represent academic, small biotech, and large pharma backgrounds. We have a nice representation of genders as well as underrepresented minorities. I believe we are very strong because of our diversity.

So You Integrated Expertise, Along With Culture.

Our quest to make network pharmacology the new paradigm in target discovery within the Janssen Immunology Therapeutic Area required bringing together two very different kinds of experts: biologists, that's my group; and computational biologists, statisticians and mathematicians who know everything about the *in silico* model of disease. Now we have a phenomenally strong team, completely integrated, and the communication is excellent — although even the languages we speak are very different. Again, that is a reflection of our diversity, not just in underrepresented minorities and women, but in different sets of expertise coming together to make something happen.

In What Ways Does Your Unit Interact With Janssen Business Partners To Apply Insights Of Patient, Customer, And Market Unmet Needs At The Level Of Discovery?

With the changes in the payer environment and the healthcare environment, there is a lot of awareness, going all the way through to discovery, of how the bar has been raised in drug efficacy. Psoriasis is a good example of a disease for which effective therapeutics already exist, and there are even more effective therapeutics now in pipelines, so the efficacy bar for psoriasis has risen much higher, and we are on the way to surmounting it. Of course, the next hurdle will be either cure or sustained remission.

Sharing This Market View All The Way To Discovery Implies Some Corporate Integration As Well.

In discovery, we certainly understand drug R&D will be conducted more and more through integrated groups with input from regulatory, market access, clinical development, and physician experience. Starting now, it will be about 15 years, if we're lucky, before one of our drugs finally comes to market. So what will the market potentially look like in 15 years' time? To be differentiated, an approved drug must not only be of value to patients and physicians, but also to the payers. We have these discussions early on in terms of mechanisms: For any given target, how is this different from drugs that we already know about and drugs that are on the market, and drugs that we are aware of in the pipeline, either in ours or competitive pipelines that have been disclosed?

Of course, we have a near-term pipeline that we need to support and move forward as well. It is a balance; there really is a commitment to focusing some of our resources on our emerging pipeline, as well as our future pipeline. L

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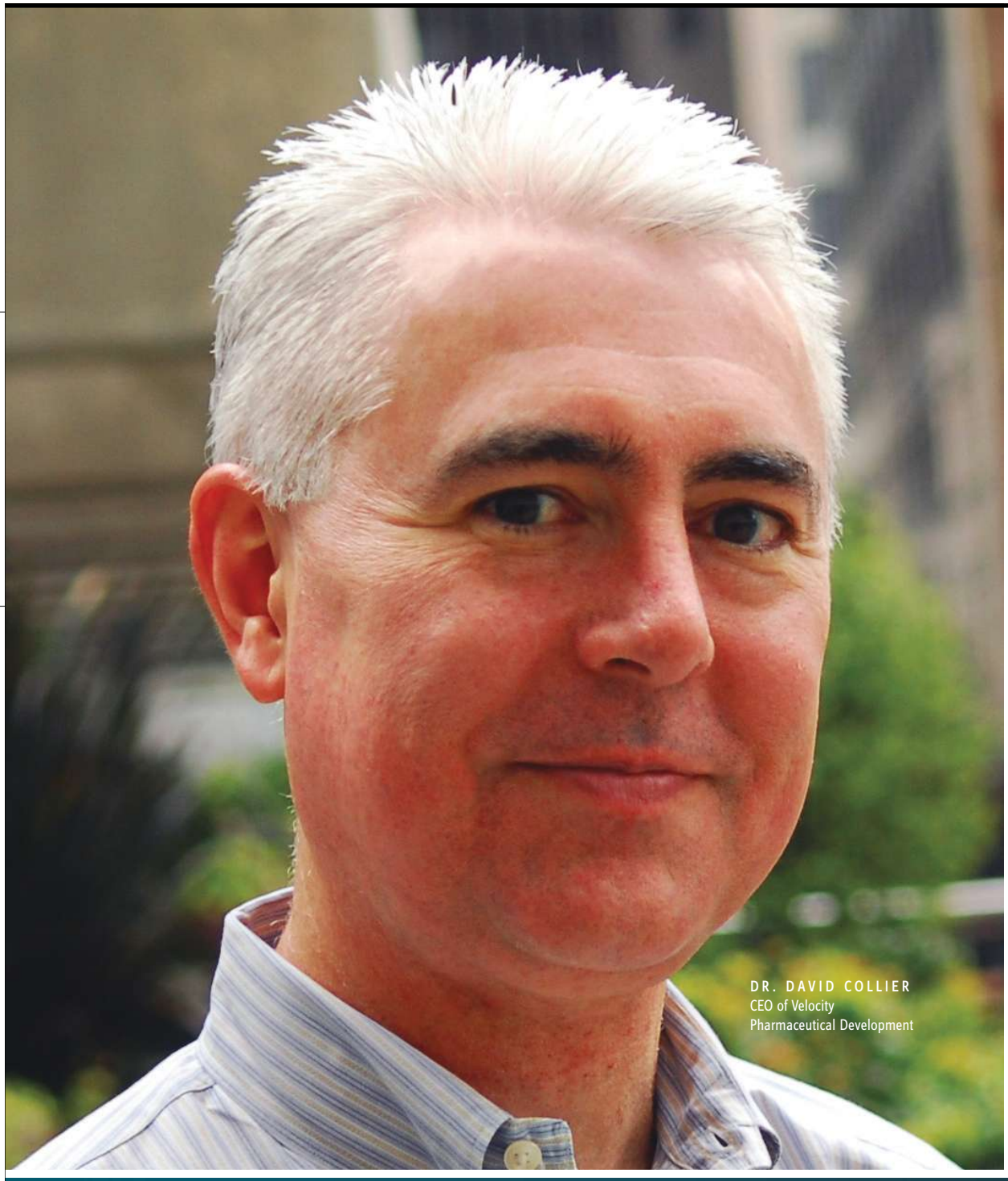

DR. DAVID COLLIER
CEO of Velocity
Pharmaceutical Development

VELOCITY: A NOVEL START-UP MODEL

THE ENTERPRISERS

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

PRIVATE COMPANY

START-UP DATE: June 2011

NUMBER OF EMPLOYEES: 12

FOCUS: Multiple drug-development "project-focused companies" run by a common expert team

In the typical start-up company, which parts are absolutely essential, and which parts are replaceable? The question really stems from a subaxiom of the virtual company concept, which normally places a small corporate-style management team at the center of operations and services supplied by outsourcing. But it leads to another logical inquiry: Does every company developing a drug actually need its own dedicated management team? That question invokes a novel answer from Velocity Pharmaceutical Development: The only nonexpendable asset is the drug itself.

Velocity starts with the drug and supplies everything else needed to support drug development — capital, management, and development expertise. It puts each of its licensed drugs inside an utterly virtual company with all the essential legal and financial wherewithal and none of the usual "encumbrances" such as permanent employees and infrastructure mirroring the standard corporate structure.

As the umbrella over a growing portfolio of such single-product, "project-focused" companies, Velocity houses a common team of managers and experts who oversee all of the entities and push each one's drug asset through proof-of-concept in humans. The company has even come up with its own descriptor for the virtual drug-development model it is pioneering: "asset-centric virtual development." With capital from the founding CEO's VC firm, Presidio Partners (formerly known as CMEA Capital) and Remeditex Ventures, Velocity has so far launched four project-focused companies, all named for aeronautic notables: Tigercat, Spitfire, Corsair, and Mustang. The first of them, Tigercat, may have a tiger by the tail with its potential blockbuster candidate, serlopitant, for chronic pruritus (severe itching), licensed from Merck along with plenty of good safety data to propel it.

"After the stock markets went crazy in 2000, there were very few IPOs for the next 13 years," says Dr. James Larrick, Velocity's managing director and one of its three chief medical officers. "So as an alternative to IPOs, as well as to the traditional start-up or the so-called virtual organization with its own exclusive management team, we came up with this project-focused company model at CMEA. In Tigercat's case, we sought to develop VPD-737 in a virtual manner and sell it after we have Phase 2 data."

SINGLE TEAM, PLURAL PACKAGES

Founders, managers, and employees of the typical life sciences company must bet their lives, careers, and fortunes on the success of drug development. Sometimes, as industry observers know well, the stakes are too high to admit defeat. Even when trials fail and the candidate is doomed, companies continue operating on their own momentum, and burning capital, beyond their usefulness. Dr. David Collier, CEO, says the Velocity model removes the motivation for ensconced management postponing the inevitable.

"Everybody at Velocity is working on all of the programs, and so everybody has an incentive to keep working on the ones that will succeed and to kill the ones that will not," Collier says. "In a traditional biotech, where there is a management team and a board of VCs who have all invested, there are perverse incentives to keep on going, to run another trial in the subset of patients where a drug may have worked, because people don't want to lose their jobs and VCs don't want to take the write-offs. It is always easier to put more money in than to just kill the whole thing. Our thesis is that we can get a lot more done with a lot less money because we only have one team spread over all the projects."

Forming a separate company around every asset also changes the way the assets are obtained, how licensors are compensated, and how the companies are financed, according to Collier. "When we acquire a drug for a virtual company we have created from scratch, we try to buy the drug by trading stock in the company. We are venture-funded and cash is expensive, so we don't want to pay $20 million up front and agree to a bunch of milestones. What we bring to the equation is a very experienced clinical development team and the funding to take the drug through clinical proof-of-concept. We divide up the ownership of the company proportionally depending on the value of the funding, the team, and the drug. If the drug is successful, the upside for its originator is owning a significant equity stake in our company. After showing the drug works, we can then sell the asset back to the originator or to another company."

THE TIGERCAT STALKS PRURITUS

In December 2014, Velocity's "project-focused" company, Tigercat Pharma, announced positive results from a Phase 2 study of its oral NK-1 receptor antagonist VPD-737 (serlopitant), for patients with severe, chronic itching (pruritus) who failed to respond well to the current standard-of-care treatments, topical steroids, and antihistamines. Two of Velocity's cofounders, Chief Medical Officer James Larrick and CEO David Collier, tell how the drug's Phase 2 results have exceeded expectations, possibly giving the company a big hit the first time out.

"Chronic pruritus will become a major indication for the pharma industry," says Larrick. "It is like other conditions that previously were considered to be an inevitable part of life until the pharma industry developed drug therapies for them – restless leg syndrome, erectile dysfunction, overactive bladder – and chronic pruritus may be one of those. We believe serlopitant is the beginning of a blockbuster category of drugs. It would be both first-in-class and best-in-class."

Collier elaborates on the potential market for the pruritus, a condition considerably more severe than most people likely realize. "Pruritus is a lot like chronic pain. It is frustrating for physicians because there are patients who are in incredible need. It destroys their lives – they can't work, they can't sleep, and in extreme cases, they're suicidal because there is nothing to help them. Pruritus is recognized as one of the big unmet needs in dermatology, and surveys suggest a multimillion patient market exists in the United States. Perhaps 20 to 30 percent of the population over age 65 has problematic itching."

Tigercat's Phase 2 trial of serlopitant was a 257-patient, four-arm, 25-center, prospective, placebo-controlled randomized trial that demonstrated high safety and efficacy, according to Collier and Larrick. Merck, from which Tigercat licensed the drug, had already tested the drug in over 900 patients in various other indications, generating a wealth of positive safety data.

"The Tigercat asset is a great example of our model's speed and capital efficiency," says Collier. "We moved it from licensing to the end of the Phase 2 trial in under two years and at a total cost of only $12 million, almost all of which was spent running the trial."

Speed and capital efficiency have become ever more valuable assets in themselves, as many life science entrepreneurs will attest. Velocity's "asset-centric" model may be paying off already in Tigercat.

Another CMO, Andrew Perlman, M.D., Ph.D., is a drug-development expert who hails from Genentech and Tularik and was also the founder/CEO of Innate Immune. But Collier gives credit for inspiring the Velocity model to CMO Edward Schnipper, M.D., who brought the seeds of the concept to Presidio in 2003. At the time, Schnipper was the CEO of Cellgate (since purchased by Progen) and confessed to having free time on his hands while waiting for results from two clinical trials conducted by a CRO.

Collier describes his approach. "Ed said, 'The way VCs fund these companies is nuts! You build this management team, you hire all these expensive people, and they are really busy for only a short time and then must wait for the trial to read out, and you're spending all of this money. Let's figure out a way you can spread me across a lot more clinical development and use my time more efficiently.' After he helped us on several other projects, we struck on the idea of having a central team to manage multiple asset-centric companies."

Although many other VCs are now experimenting with capital-light companies in virtual development of novel drugs, Collier believes Velocity has the "most virtual" model. He mentions Atlas and Index Ventures as firms that employ a core consulting team to advise or sometimes run the companies they fund. But, he argues, the economic incentives for those people are still largely tied to the fate of particular products. In another example, Lilly and TVM Capital have partnered to select certain drugs out of Lilly's pipeline, use the fund's money to develop the drugs into proof-of-concept, and then give Lilly an opportunity to buy them back again. Similarly, Swiss-company Debiopharm combines expertise along with a pool of money, licensing in drugs from the outside and developing them within the company rather than creating separate legal entities for each drug as does Velocity.

"Putting each drug inside a separate company makes it a really simple package for a pharma company to acquire," he says. "Pharma companies are accustomed to buying biotech companies, but the part they don't like is the people and all of the liabilities that go with them. So we give them a company that has never had any employees or even an office. There is nothing in the deal other than the IP for the drug, the clinical data, and the contract with the CRO and the contract with Velocity. Due diligence is clean and simple. It also works for financial reasons because Velocity is funded by only venture capital."

Collier explains that, if a pharma company were simply to license the drug, it would wind up in a double-taxation situation, but in the Velocity model, it would just buy the virtual company outright, which is not a taxable event by itself. The money exchanged would flow back as a capital gain to the investors in the fund, leaving only one level of taxation instead of two.

Collier emphasizes the unique aspects of the Velocity model. "Unlike a lot of the other variations on our model, the team we've built here is a clinical development team, and the expertise around the table is in developing drugs. Many of the other

COMPANIES WITH WINGS

Velocity has officially launched four virtual companies, all with their aeronautic names, but it has released detailed public information on only two of them, Tigercat and Spitfire. All of the companies besides Tigercat are still at the preclinical stage. Among the other three, Spitfire is furthest along, with a novel dual GLP-1/glucagon receptor agonist for treatment of type 2 diabetes and obesity. Tests on animal models of those two conditions have shown significant weight loss and glucose reduction following treatment with advanced drug candidates.

The most advanced lead is a novel peptide compound with the extended-release technology, EuPort, licensed from its developer EuMederis. With the drug, Velocity hopes to match better-than-standard glycemic control with significant weight reduction through a weekly subcutaneous injection.

"Our current thinking is we need to take this peptide into a human proof-of-concept trial before we sell it, and we're still trying to figure out exactly what that study needs to look like," says CEO David Collier. "So we're talking to pharma companies to get their input on what data they would want to see."

Velocity has not yet revealed details of its plans for the remaining two companies, Corsair and Mustang. It says Corsair is developing a pulmonary disease drug, but will not be releasing more information until at least the end of 2015. Mustang remains shrouded in confidentiality.

programs are run by VCs who have investing experience, but no real drug-development experience. But I am the only VC in the crowd here; everyone else has a long history of successfully developing drugs."

It will likely be many years before the success or failure of Velocity plays out and we know whether its model actually worked as planned. Meanwhile, many people will be watching how well the company implements its "asset-centric virtual development" concept, which will continue to challenge the conventional notion of life sciences start-ups, and we shall see what is really essential and nonessential in a virtual company. L

Do you have something to say about Velocity and its start-up drug-development model? Please post your comments online with this article under Current Issue (June 2015) or Past Issues at lifescienceleader.com.

Lilly's Approach To Discovery Via Collaboration

ED MISETA Executive Editor @OutsourcedPharm

Being a large pharmaceutical company located in the Midwest has some advantages, but the location is still evolving as a recognized pharma or bio hub. Today's drug development challenges are also more complex, and some cannot be solved by one company alone. That means pharma firms such as Eli Lilly and Company have to perform research without boundaries, so as to access the best innovators and thought leaders wherever they exist.

Andy Dahlem, VP and COO of Lilly Research Labs, notes the company's long history of success has been built on collaborating, specifically building relationships between internal scientists and the external world. Those relationships have helped, for example, with solving problems related to molecules in development. But having these relationships also provides access to individuals who might like to collaborate with Lilly on developing their own molecules.

"In exchange for that development opportunity, we offer much more than just financial remuneration," notes Dahlem. "We offer true collaborations with our scientists in the development of molecules and the planning for bringing them forward. We believe that approach has been beneficial for all parties involved."

Throughout its history, Lilly's success has been contingent on its ability to both innovate internally and acquire molecules from external sources. About half the medicines Lilly has marketed to patients in the last two decades were developed via some form of external collaboration, extending from the earliest parts of the discovery effort through to the entire discovery and development process.

As a result of that history, Lilly now has a diverse set of long-term public/private partnerships in place, which the company views as a core part of its business. Scientists are given the time, access, and permission to build these relationships. Those collaborations that are built in the precompetitive space will provide both entities the opportunity to continue to work together as additional therapies are discovered.

BIG PHARMA PARTNERING WITH BIG PHARMA

Dahlem believes finding a treatment for diseases such as cancer and Alzheimer's is akin to fighting a war. That means companies will increasingly find themselves seeking allies to help in the struggle. That also means Big Pharma companies will need to align resources with other Big Pharma companies. It is not unusual to see press releases announcing a Lilly collaboration with BMS or Merck on a combination therapy. For diseases such as cancer, if two large pharma companies each hold a piece of the puzzle, partnering may be the best option to save and prolong human lives.

"We are always looking for new and innovative ways to collaborate, particularly in the precompetitive space," says Dahlem. "We locate potential partners, identify targets, and then accelerate the development of a single agent. We take those back to our labs and are off to an aggressive start as a result of the effort. This partnering can also take the form of combination therapies, where we partner with another pharma company possessing a molecule that we think might be effective in combination with ours."

In his role as SVP for corporate business development at Lilly, Darren Carroll works with the teams responsible for all transactions, from the early stage of technology through to the latest collaborations, partnerships, mergers, and acquisitions. He notes the company was also the first to establish a separate office to manage all alliances.

Over the last five years, Lilly has been doing a lot more partnering with other large phar-

"Resource allocation is a struggle for every pharma company that has an active and productive R&D engine."

DARREN CARROLL
SVP for Corporate Business Development at Lilly

ma companies. In those areas where Lilly has significant expertise, the company has increasingly been approached by experts in other companies hoping to develop a relationship. Two examples are a collaboration with Boehringer Ingelheim for the development and commercialization of several diabetes medicines and an agreement with Pfizer to codevelop a nerve growth factor inhibitor molecule that is the first in a new class of potential pain medicines. More recently, the company entered into a collaboration agreement with AstraZeneca on a BACE (beta secretase cleaving enzyme) inhibitor, which is in Phase 2 development for Alzheimer's disease.

According to Carroll, Lilly will focus its collaboration and external innovation efforts on five therapeutic areas. Three are core therapeutic areas for Lilly: diabetes, oncology, and neurodegeneration. The other two are emerging areas in which Lilly has molecules in the pipeline: immunology and pain. How the molecules in those emerging areas progress will determine how aggressively the company will seek external innovation to supplement its efforts.

"Resource allocation is a struggle for every pharma company that has an active and productive R&D engine," he says. "It's our own capabilities in science, in fact, that are key to helping us identify external innovation opportunities, as well as how to best shape them."

"The goal of these collaborations, our goal, is to improve the lives of patients," says Dahlem. "Sometimes that will mean taking a Lilly drug, other times it will mean taking another company's medicine. But sometimes the best option for the patient is taking two medicines produced by different companies. Many of these collaborations occur in the oncology space, and what we need to do is determine whether or not there are synergies that can be accrued by taking two agents in combination with each other. The only way we can determine that is by having scientists from both companies working together."

ALIGNMENT OF STRATEGIES AND CROs IS VITAL

Most large pharma companies have efficient infrastructures in place that emphasize quality and patient safety in their operations. But as you might expect, bringing the two companies together to collaborate on a project is not an easy process. Knowing what issues might arise, and preparing for them ahead of time, will make for a smoother collaboration.

"One of the most important things you need to worry about is making sure you're strategically aligned on how the combination of your medicines will benefit the patient," says Carroll. "It is important to determine if your research programs can work together in a complementary fashion. Determining what tumors are of interest to each company should be an integral part of that process, but you must also ensure that both companies are pursuing the same end goal."

Determining the effectiveness of a combination therapy requires additional research to determine if the two medicines together will still be as safe and effective as they are individually. This will entail additional data generation and investment. There will also be different approaches to development that have to be considered. Those approaches will determine how companies will begin to explore the level of proof necessary to make the next series of investments.

"One company might want to perform smaller, exploratory studies before making a larger investment, while another might prefer to jump right in," notes Carroll. "I don't think too many companies will take a one-size-fits-all strategy approach. You have to make sure the two companies' philosophies align."

Another challenge has to do with different CROs being used by each company. One solution might be to use two or more CROs to perform different aspects of the clinical study. For example, one CRO may recruit and treat patients, while the other performs the clinical laboratory analysis. "The synthesis of the information is often done by the sponsor," notes Carroll. "In our experience, it is more likely that the collaborating companies would prefer to continue to keep working with multiple CROs on specific components of the study, where each CRO has unique qualifications or capabilities, than to select one over the other."

PROJECT AND STEERING TEAMS DRIVE DECISIONS

Another action that carries a high degree of importance when partnering with companies of any size is establishing, early on in the process, how difficult decisions will be made. When an impasse is reached in a decision-making process, such as choosing a CRO, it is best to leave the decision up to a joint steering committee. There should be agreement on who gives input and who will be on the committee and, when there is an impasse, how the final decision will be made.

Generally there is a project team that drives the decision making within the collaboration, and it is made up of individuals from functional areas such as quality, legal, and regulatory. That team makes decisions on how a trial should be run. If two different perspectives arise and a decision has to be made at a higher level, that is when the joint

"We are always looking for new and innovative ways to collaborate, particularly in the precompetitive space."

ANDY DAHLEM
VP and COO of Lilly Research Labs

steering committee would be engaged. Members of that committee would generally be senior leaders within the organizations.

Any partnering decision will have an impact on numerous functional areas (quality, regulatory, supply chain) within a company, so be sure to keep those areas involved in the partnering process. Lilly has an internal system called Linkage Hub to ensure everyone impacted by a collaboration is kept informed. Through the Linkage Hub collaborative, all pertinent documents are shared with representatives of every key function, geography, and business unit within the company in a timely fashion. These knowledgeable representatives serve as key communicators between project teams and functions and ensure alignment and collaborations occur effectively.

Linkage Hub is jointly run between the teams under Dahlem and Carroll. "We have both scientific and business leadership running Linkage Hub to ensure we have the maximum input possible," notes Dahlem. "With these types of deals, we are well aware that the devil is in the details. We want to maintain a project team that is paying attention to the details and quickly driving efforts through to completion. Linkage Hub is made up of the individuals accountable to ensure that happens on a very reliable and particular basis."

Finally, continuous improvement is important to Lilly in refining its collaboration efforts. To continually improve, Lilly employs partner surveys that assess how the company is performing on a number of partnership factors. "I think this is something that differentiates us from some of our peers," says Dahlem. "We report the feedback and findings in a spider-web diagram. We look at the areas where we agree and disagree, and then we work to make improvements. This has been an effective tool for us in the development and implementation of strategic alliances."

The spider diagram has three areas of focus: cultural fit, strategic fit, and operation fit. The cultural category looks at knowledge management and flexibility. Strategic fit examines commitment, strategy, and trust/fairness. Operational fit is the most encompassing of the three areas and examines communication, conflict management, decision making, leadership, performance management, roles, skills/competence, and team coordination.

Dahlem notes as a result of these surveys, Lilly can quickly see where they agree or disagree with a partner on performance of the collaboration. The company can also identify root causes to improve performance. "Effective communication is at the core of strong collaborations, and these spider diagrams give us direct feedback to aid communication at all levels," he says. "It's this feedback that will enable us to continue to be a strong collaborator well into the future."

Collaborations Will Drive Oncology Research

Sue Mahony, SVP of Eli Lilly and president of Lilly Oncology, expects Big Pharma collaborations in particular will be critical for companies looking to stay on top of innovation in key therapeutic areas, for instance, oncology. She notes combination therapies will be key to addressing tumor heterogeneity and the inevitable resistance that is likely to develop to even the most promising new tailored therapies.

Last year Lilly announced a collaboration with Immunocore that gives Lilly exclusive access to a new biology that includes three distinct targets. In 2014 the company also expanded its existing collaboration with Zymeworks to develop potential cancer immunotherapies. And earlier this year, Lilly announced it will collaborate with Innovent Biologics to support the development and potential commercialization of at least three cancer treatments over the next decade.

"Oncology collaborations are designed to give us more information about the potential of combination therapies, which will be instrumental to the future of cancer care," she states. "Cancer is not one disease, but rather more than 200 diseases, all of which have different causes and treatments. As such, cancer will remain a complex and difficult-to-treat disease area for many years to come. We don't expect that a single technology will modify this situation in the next decade."

WHAT DO YOU LISTEN FOR IN A CRO?

Ideally, you want to hear that the professionals you work with care about more than their own processes. That they take the time to understand your needs and learn about your unique situation. That the value they offer isn't just a wide range of services, global footprint and deep experience, but the ability to draw on that vast skill set to craft a customized engagement perfectly matched to your vision. Sound good? Let's talk.

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Is Pharma Ready For The Mounting Price Transparency Storm?

KEN CONGDON Executive Editor @KenOnPharma

Perhaps the biggest disruptor in the healthcare industry in recent years has been the concerted effort to bring transparency to the pricing practices that have historically been shrouded in mystery. This initiative came to a head in 2013 when CMS (Centers for Medicare & Medicaid Services) released hospital chargemaster data for the 100 most common DRGs (diagnostic related groups) for 3,400 hospitals.

This data represented 92 percent of all inpatient charges for fiscal year 2011. A month later, CMS released similar pricing information for outpatient procedures. The price transparency movement continues to pick up steam in the provider sector. From where I sit, escalating external demands on the pharmaceutical industry to similarly disclose cost and pricing logic is, quite simply, unavoidable.

FEDERAL & STATE DEMANDS FOR PRICE TRANSPARENCY ON THE RISE

It's no surprise why price transparency has taken center stage in healthcare. With healthcare costs totaling more than $2.9 trillion annually in the U.S. (17.4 percent of the GDP) and growing at a steady pace, it's clear that our traditional healthcare model is no longer sustainable. Furthermore, with more Americans opting for high-deductible healthcare plans, patients are absorbing more and more out-of-pocket healthcare expenses.

While the cost of prescription medication accounts for only a little more than 9 percent of this $2.9 trillion annual healthcare expense, the relentless media exposure and public outcry surrounding the perceived high cost of prescription medications have placed the pharmaceutical industry firmly in the country's transparency crosshairs.

Recently, CMS responded by releasing data that provides details on the $103 billion that Medicare's Part D prescription drug program spent in 2013. The data shows the names, locations, and specialties of physicians and healthcare organizations that submitted drug claims to Medicare during this time period and also outlines which drugs were most commonly prescribed and which cost the program the most. Some CMS officials hope the release of this information to the public will reignite debate over whether Medicare Part D should be able to negotiate discounts for drugs, given that billions of dollars are being spent when cheaper alternatives exist. (Medicare is currently prohibited from negotiating discounts between private plans and drugmakers in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003.)

Transparency pressure on the pharmaceutical industry isn't just coming from federal entities. Over the past several weeks, a growing number of state legislatures — including California, Massachusetts, North Carolina, and Pennsylvania — have introduced bills that would force the pharmaceutical industry to disclose their costs to justify pricing. These bills vary slightly from one to the next. Some require drugmakers to report profits and operational costs for any medicine that costs more than $10,000 a year, while others demand this information for all medicines regardless of price.

FOR PHARMA, THE BEST DEFENSE MAY BE A GOOD OFFENSE

Both federal- and state-driven pharmaceutical transparency initiatives are gaining fervent backing from business groups, consumer advocates, and health insurers alike, which could prove problematic for pharmaceutical manufacturers. Drugmakers have always maintained that the prices charged for an individual drug are not a reflection of development costs, but are based on a combination of therapeutic value, market size, usage, patent life, competition, and other factors. Moreover, pharmaceutical

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leaders claim that many of the demands issued by state legislatures simply cannot be met. Namely, providing development costs for some drugs may not be possible when research may have been simultaneously conducted on other medicines that ultimately failed.

While the arguments posed by the pharmaceutical industry have merit, they are unlikely to quiet legislators and the American public for long. If you haven't already begun to strategize how to address mounting price transparency demands, it's high time that you did. The most immediate response to transparency made by many drugmakers has been to fight these measures in a court of law. However, this approach doesn't seem like a long-term solution to the issue. These often lengthy legal battles carry a significant price tag in their own right, and it's unlikely that all drug-pricing legislation will be defeated by pharmaceutical interest groups. At some point in time, it's a safe bet that pharma companies will be forced to disclose cost and pricing methodologies at either the state or federal level. The transparency issue isn't going away, and drug manufacturers need to be proactive to succeed in an era of heightened scrutiny and accountability.

Dealing with transparency is not an entirely new proposition for pharmaceutical manufacturers. Over the past couple of years, drugmakers have been providing data to CMS regarding their financial relationships with physicians in compliance with the Sunshine Act as part of the ACA. The act itself has required drug companies to change their way of thinking — taking information that has historically been kept confidential and packaging it in a way for public consumption.

Complying with drug cost and pricing transparency demands will likely prove to be considerably more complex for pharmaceutical companies and have a greater impact on their day-to-day operations and future growth strategies. The effort will undoubtedly require universal process enhancements and an intensive change management effort.

This, at least, is how the transparency movement is impacting the health provider market. After hospitals got over the initial shock of having their top-secret chargemaster data suddenly made public by CMS, they began the painful process of gaining a granular understanding of their true cost-to-charge ratios. This is something that many hospitals had rarely done because they seldom had to justify their pricing. This effort is now alerting healthcare providers to weaknesses and inconsistencies in their cost structure and forcing many to change their pricing logic and update their chargemasters.

Surviving, and ultimately thriving, in an era of increased price transparency requires radical change. The hospitals that are succeeding are learning to do more with less and eliminating as much waste as possible from key processes in order to maximize efficiency. In many instances, healthcare providers are finding innovative ways to cut costs and lower prices while maintaining desired profitability.

A similar path will need to be followed by pharmaceutical manufacturers as price transparency demands continue to gain momentum. At the very least, drugmakers should:

> *"The relentless media exposure and public outcry surrounding the perceived high cost of prescription medications have placed the pharmaceutical industry firmly in the country's transparency crosshairs."*

1 BE PROACTIVE

Begin gaining a granular understanding of costs at every phase of the manufacturing process (e.g., R&D, supply chain, logistics) and start packaging this data in a manner that's fit for public consumption.

2 ADJUST YOUR MESSAGING (IF NECESSARY)

If (or more likely when) your organization is required to divulge drug costs and pricing rationale, be prepared to combat push back from both federal and state legislators, as well as the general public. Be able to defend your current pricing logic with carefully prepared evidence and messaging.

3 LOOK FOR OPPORTUNITIES FOR GRANULAR SAVINGS

Like hospitals, pharmaceutical manufacturers should immediately begin looking for ways to cut costs and eliminate waste from every phase of the drugmaking process in an effort to offer more competitive prices to patients without sacrificing profitability. This effort should include application of lean methodologies, organizational restructuring, and potential process automation through effective application of IT solutions.

One thing I know for sure is that the healthcare provider space and the pharmaceutical industry are inextricably linked. Moreover, these markets have a shared focus — improving the lives of the patients they serve.

Most would agree that the quality of healthcare in the U.S. is among the highest available in the world. However, the affordability? That's been a bone of contention for years. The government and other key stakeholders are now pressuring health providers and pharmaceutical companies to improve on both a cost and quality front. Many believe patients deserve better, and I would have to agree. L

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What To Consider When Designing An SLA With A CRO

DEBBIE DWYER & JONATHAN LEE

Apart from defining the expectations for FSPs (functional service providers), the pharma industry's use of SLAs (service level agreements) has not been commonplace despite the tangible benefits these documents offer. In essence, the SLA defines critical metrics and levels of expectations for service, as well as outlines incentives and disincentives for meeting/missing those metrics and expectations.

But to avoid disputes between the two parties, it is essential that the expected level of service be clearly defined for each service provider *in writing* prior to initiating work.

START BY DEFINING METRICS

The initial conversation with a service provider should include a discussion of the metrics deemed critical to the success of the outsourced program or service. Those metrics should reflect your business requirements, be economical to measure (e.g., calculate performance) and report, and be simple to understand. Regarding the latter, everyone should agree that what needs to be measured can be easily written down. The Everest Group suggests following the acronym SMART when defining performance metrics:

- **Specific:** The SLA answers questions of who, what, when, where, why, and which.
- **Measurable:** The SLA should include specific criteria for measuring compliance.
- **Achievable & Realistic:** Unrealistic requirements are not conducive to good outsourcing relationships.
- **Timely:** Where appropriate, deadlines and time constraints should be noted.

Of course, for any outsourced program to succeed, you must have explicit endorsement (either active or vocal participation) of senior management and decision makers within each organization.

AVOID COMMON PITFALLS

When defining what is acceptable regarding your SLA, beware of pitfalls such as expecting more of your service provider than you may expect of your own staff or driving toward perfection. While these may be valid goals, you must bear in mind the inherent cost of each position. For example, if your internal team states it is critical for them to have final monitoring trip reports to review within five business days after the visit, that may not be the SOP timeline for the service provider. Therefore, your internal team needs to establish reasonable expected service levels and see how those expectations line up with the service provider's capabilities.

Ultimately, you need to gain trust to put this type of agreement in place. To do so, have governance meetings on a regular basis and ad hoc discussions as needed. For any of these meetings, develop agendas, take detailed minutes, track follow-up items, and have someone in charge of delegating. Doing so ensures these discussions progress rather than becoming a time burden on an already busy workforce.

THREE SLA MODELS

In our experience, it is advantageous to incentivize your service providers to meet or exceed your expected performance levels. While global CROs may have experience with performance metric regimes, the SLA framework can still be far from standard and generally requires tailored solutions. The following are three examples of models we have utilized during our careers.

Shared Incentive Pool

For a smaller-value agreement with, for example, a regional CRO or specialty vendor, we often implemented an agreement we called a shared incentive pool. In this scenario, both parties contribute to a pool that is paid out for key milestones but reduced for performance shortfalls in critical areas. The goal is to have the regional CRO focused on achieving/beating the milestones, but to do so in a way that does not compromise quality.

Full SLA

A "full SLA" can be used for a larger-value agreement with a major CRO or global service provider. Within this structure, service levels are either critical performance indicators (CPIs) or key performance indicators (KPIs). The CRO will perform the services at or above the levels of performance indicated by the CPIs and KPIs. If the CRO's performance falls below these performance levels, the CRO will promptly take the corrective actions. A CRO's failure to meet a CPI results in a financial penalty (credit to sponsor), which escalates for major failures or repeated service failures. These penalties are automatically applied to the labor portion of monthly invoices.

KPIs do not have financial credits associated with them, but are important as early-warning indicators regarding problems with meeting CPIs. KPIs and CPIs may be "promoted" and/or "demoted" at the sponsor's discretion with 60 days advance notice. The agreement also may

"It is essential that the expected level of service be clearly defined for each service provider in writing prior to initiating work."

provide a bonus for completing milestones early, but does not provide a bonus for exceeding the performance service levels. Also, it should be noted that the bonus will not equal the potential financial penalty that the CRO can accumulate.

Compact SLA

This is a "lighter" version of a full SLA; there may be fewer CPIs/KPIs and a smaller bonus regime focused on key metrics. The compact SLA is put in place with a CRO or specialty vendor when the value of the agreement is small. Still, the CRO will perform the services at or above the levels of performance indicated for the CPIs and KPIs. The same penalties of a full SLA apply.

SLAs ARE MUTUALLY BENEFICIAL

In reality, it is not in anyone's best interest to apply disincentives when the agreed-upon service levels are missed. The sponsor needs the service provider to deliver on its commitments, while the service provider needs a clear view of the sponsor's expectations and expected revenue from each program. In summary, SLAs provide a framework and structure for:

- aligning the contracted services with the sponsor company's requirements and expectations
- documenting acceptable levels of service and targeting specific outcomes required for each study
- highlighting the most critical goals and measurements
- focusing a service provider's attention and resources on the desired outcomes
- monitoring the agreed-upon levels of service
- managing the consequences of any substandard performance. L

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With 25 years' drug development experience, Jonathan Lee is currently VP of development operations at Cidara Therapeutics focusing on antifungal therapies.

Moving Human Clinical Trial Design Into The 21st Century

KEREN SOOKNE Contributing Writer

The pharmaceutical industry is facing a productivity crisis, with current trial design flaws leading to extremely high attrition rates. Despite increased R&D spending and advances in molecular biology, data collection, and analytical technologies, the number of approved medicines remains relatively constant.

The failure rate of new drugs is alarming, particularly in Alzheimer's disease, with a recent review of Alzheimer's drug clinical trials from 2002-2012 reporting a success rate of 0.4 percent.

Clearly, there seems to be a translational disconnect between preclinical animal models and clinical outcomes, especially in disorders of the most complex organ in the human body — the brain. But some pioneers are embracing a technology that makes use of vast new data libraries and innovative approaches to identify viable candidates more efficiently than ever before.

AVATARS

The word *avatar* conjures images of blue hybrid human-aliens in movies or the cartoon vaguely resembling you in a video game. But this is a much different take: a digital human avatar, or virtual human patient, that could address the issue of personalized medicine, allowing new medications to be extensively tested *in silico* before they enter into human trials.

A virtual patient sounds a bit far-fetched, but it's really a new application of a traditional concept. "We looked at how other industries — chemical engineering and aeronautics — deal with new problems by using advanced modeling and simulation as much as possible. By prototyping *in silico* before building, their success rates are much higher than in pharmaceutical R&D," explains Dr. Hugo Geerts, chief scientist at In Silico Biosciences (ISB), a small company founded in 2002 based on the concept of quantitative systems pharmacology (QSP). With QSP, advanced computer modeling of biologically realistic neuronal networks is used to simulate the impact of digital pharmacological interventions on emergent properties.

Dr. Geerts is no stranger to the use of predictive modeling and simulation in drug development. His years of experience in drug discovery and development in Alzheimer's disease with the legendary drug hunter, Dr. Paul Janssen, (along with degrees in theoretical physics, medicine, and biophysics) put him in the perfect position to develop the technology for extremely complex CNS research. "A lot of academic work over the last 70 years has been done in computational neuroscience. Alzheimer's was a great area to start."

With the goal of reengineering drug discovery operations for CNS diseases, Dr. Geerts and his colleagues at ISB created a humanized computer-based integration of physiology and pharmacology knowledge, molding existing information into a pharmaceutical research tool. In contrast to bioinformatics, they introduced the expertise of neurologists, neurobiologists, and neuropharmacologists into the platform. Timing of action-potential firing is calculated as electrical activity of specific brain regions that drive human behavior. The result is a virtual human patient, a platform on which they can test pharmacological activity of a new drug to predict how it might perform in human clinical studies.

"In 2002, the idea was far too hypothetical and far-fetched," Hugo muses. Biologists didn't believe this was viable, and, because it fell between the categories of academic and real-world projects, his team was unable to secure NIH grants or other financial VC support.

At present, ISB has worked with about 10 companies, ranging from Big Pharmas like Roche and Pfizer, to small and mid-size companies, and non-profits (including the Michael J. Fox Foundation), with success stories in which their methods have been used to predict clinical outcomes.

FINANCIAL (AND SAFETY) BENEFITS OF MODELING AND SIMULATION

Simply put, the technology improves trial design because its results are often closer to clinical reality than those extrapolated from preclinical

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animal models. According to Dr. Richard Peck, global head of clinical pharmacology at Roche, "More realistic modeling means trials can be designed better, with increased efficiency and reduced costs, leading to better outcomes. There's less waste on failures, and trials are safer."

Success rates with the ISB platform include two blind and prospective predictions of Phase 2 clinical outcomes in schizophrenia and a correct but unexpected clinical Phase 1 proof-of-concept prediction for a new compound in Alzheimer's disease:

- In the two schizophrenia cases, savings could have ranged from $20-$50 million had the ISB platform been used prior to human trials, and there was a missed opportunity to develop a better backup compound.
- With the Alzheimer's drug, the platform identified a different patient population that could have rescued the already large investment at that point.

Note that in these situations, no clinical data was available for the drugs under development; this illustrates the difference between predictive modeling with QSP versus more traditional PK/PD (pharmacokinetic/pharmacodynamic) modeling that relies upon *existing* clinical data with the actual (or a similar) compound under development.

DRUG INTERACTIONS

Though it may seem counterintuitive for some, virtual human patients can provide much more realistic predictions with comedication simulation. Dr. Geerts says, "In rodents, we take the rather naïve approach of testing one drug at a time. With advanced modeling, we can take multiple medications beyond the test drug into account." For example, Alzheimer's patients often take a myriad of drugs (sleep aids, antidepressants, antipsychotic drugs for behavior, etc.), resulting in many complex interactions, which rodent trials simply cannot replicate.

Currently, an ISB test platform can accommodate up to six different drugs and can include four different common human genotypes that have been shown to affect clinical outcomes. Without advanced modeling, clinicians may not be able to predict adverse comedication reactions or the impact of the genotypes, with the potential for putting patients at risk and failing trials.

> *"I suspect many drugs that appear to fail actually do work, but only in a subset of patients."*
>
> **RICHARD PECK**
> Global Head of Clinical Pharmacology, Roche

RIGHT TARGET(S), RIGHT PATIENT(S)

Researchers from AstraZeneca recently performed a review to understand the major reasons for project termination over a five-year period. They identified the importance of "right target" and "right patient" as features of projects that correlated with successful outcomes.

Along these same lines, Dr. Geerts postulated that the high degree of failure in CNS trials may be a result of the "extreme complexity of the human brain neurobiology, and ... that the clinical outcome is driven by emergent properties of neuronal circuits, rather than by a single target." It's highly unlikely that affecting only a single target in this complex network of interacting circuits can result in major clinical change; hence the need to start considering rationally designed polypharmacy early in drug discovery. The mechanism-based computer model, constrained with clinical data, can help scientists understand these complex interactions because the biological rationale and assumptions are clearly formalized.

Beyond the complexities of the "right target(s)," variability between patients is a tremendous challenge in drug development. Modeling has shown that some Alzheimer's patients progress more rapidly, while others progress slowly. "Here's a case where we can use modeling to define the patient population we should be treating: the fast progressors," Dr. Peck says, adding, "If all the patients are put into one category, there's a high probability that the study will fail to find the effect of the drug, because the benefit in high progressors might be masked by the noise from the lack of benefit in slow progressors."

He says, "I suspect many drugs that appear to fail actually do work, but only in a subset of patients, and we have not found that subset. Modeling will increase success rates because we'll better understand which patients should be getting the drugs. By studying our drugs in those patients, we'll *find efficacy* rather than missing it."

The QSP platform helps identify possible reasons for failed clinical trials to avoid repeat mistakes (another common engineering principle). By simulating the individual trial patients, the platform can examine whether the dose was optimal, whether there was an imbalance between treatment in patients' comedications or genotypes, or whether the drug's off-target pharmacology affected the clinical readout.

PATH TO ACCEPTANCE

Though early adopters are finding success, there are hurdles to overcome in the industry. Dr. Geerts cites fears associated with lack of biological knowledge to parameterize the computer model and, surprisingly, a fear of advanced mathematics among some biologists. He says, "We know about physics and engineering principles, but people say we don't know enough about human brain biology to make a model." Though we have much to learn about human biology, he feels that the available information is not used to the fullest extent in traditional trial design. "Engineers didn't wait for the Grand Unified Theory to develop extremely useful tools."

The ISB team encourages scientists to formulate their own hypotheses to be implemented into the mathematical platform. "In this regard they start owning the model, which is crucial to broader acceptance of this technique and is more

difficult to achieve with the more traditional 'hypothesis-free' and relatively abstract approach of bioinformatics."

Timing is important. Modeling provides the most value when it's used early on, preferably at the point of target validation. He explains, "Sometimes we come in on a project and predict that the compound needs a certain dose, but it doesn't match with what the company determined based on rodent models. Our predictions are often closer to reality than the extrapolations of rodent models, so it makes sense to start modeling early."

CONVINCING DATA

Just as the industry transitions from using X-ray to MRI data in clinical trials, comparable data between modeling predictions and actual clinical trial results is needed to increase user confidence.

Leaders in the Alzheimer's field have formed a working group, tentatively named the Brain Health Modeling Initiative (BHMI), with three main goals:

1. **Define** the need for modeling and simulation technology.
2. **Introduce** biological complexity rather than simple linear hypotheses; go from correlation to causation.
3. **Raise awareness** of successful applications, and invite scientists with a new skillset and fresh eyes to join the movement.

The approach was presented at the 2015 NIA Disease Research Summit, and the working group has a toolbox for new adopters in the works, with plans to publish a series of papers outlining the challenges and possible solutions in the near future.

FUTURE STATE

As acceptance grows, Dr. Geerts sees the potential for personalized medicine beyond drug development. Imagine your doctor creating a model that takes your unique information (genome sequences, imaging, biochemical lab work, etc.) into account. "Our ultimate goal," he says, "is to create an individualized mechanism-based human avatar based on 'pan-omic' data, where we could systematically test all available therapeutic interventions to find the best treatment with the best benefit-risk ratio."

Does the technology sound revolutionary? Sure. But so did most of the modern tools we've come to rely on. For now, with companies risking billions of dollars on development, the need for cheaper, faster, and safer trials has never been more urgent. By using virtual patients to test real-world scenarios on the right patients and the right targets, trials can be designed better, resources can be allocated appropriately, and attrition rates can be reduced. L

Funding Your Biotech: Go Beyond The Traditional IPO

DAVID DIAMOND

It's no secret that the biotech IPO market has been "on a tear" of late. While it's brought greater exposure to the industry, it also has afforded investment banks the luxury of being hyperselective when deciding which biotech companies to work with and to bring public.

Because the market has been so hot for so long, no one knows when the window will shut. That being said, if a company has good technology and wants to go public, now is the time.

However, the competition is fierce, and investors are unwavering in their desire to work with top-notch companies, including those that can withstand scrutiny of their clinical data, carve out a large enough market niche for their drug, and/or offer a robust pipeline of drugs or medical devices. This doesn't mean that biotech companies are left without options for funding, nor does it mean that they will never go public. Rather, they need to consider alternative lending sources. Here are a few options:

1 VENTURE CAPITAL

The number of VC capital firms investing in early-stage biotech has shrunk significantly during the past several years, with some going out of business and others taking the safer route of investing in more mature companies. Yet, there is still VC funding available for the right start-ups. Those remaining early-stage VCs generally look for companies that have CEOs or management teams with proven success records, which makes it easier to fund-raise and go public more quickly. In turn, this means the VC will see a return on investment more quickly. An example of this is serial biotech entrepreneur Rich Heyman, who was founder and CEO of Aragon Pharmaceuticals. He sold Aragon for $1 billion to Johnson & Johnson, then quickly started Seragon Pharmaceuticals. Because he had a proven record of success with Aragon, VCs immediately put money into his deal. He sold Seragon for $1.7 billion in 2014 to Genentech.

2 GOVERNMENT GRANTS

If a biotech company doesn't want to go public or work with a VC firm, another option is to apply for government grants, which include funding from Small Business Investment Research (SBIR) or the Defense Advanced Research Projects Agency (DARPA). Companies also can receive funding as an incentive for locating in science parks that have been set up in cities across the United States, as well as in certain cities in Europe. We had two biotech clients; one went to a business park in Holland and received $3 million dollars in grants, and another went to Austin, Texas and received a grant of several million dollars.

3 BIG PHARMA

Big Pharma companies are another source of funding. These companies often will invest in very early-stage drug companies, fund them through drug development, and then buy them out without the company ever going public.

4 ANGEL INVESTORS

Companies can get funding from friends, family, and angel investors. Angels can be seen investing in both small and large deals, but they generally invest in early-stage companies. The Internet is the best place to research angels, but other good sources for contacts are accountants, attorneys, and banks that specialize in biotech companies.

5 ALL OF THE ABOVE

Biotech companies shouldn't feel that a funding source should fall into one category or another; many companies have been funded by a combination of all of the above. There are no restrictions on the number of sources that can offer funding.

Biotech CEOs should not get caught up in the frenzy of the stock market, as valuations of public companies are often inflated, setting unrealistic expectations for private companies. Rather, CEOs need to be pragmatic when it comes to valuations. Though fundraising is difficult, with a little creativity and an open mind, funding can be secured, and an IPO can be within sight. L

David Diamond, CPA, is a managing director of CBIZ MHM, LLC, a national top 10 accounting and professional services provider, and the National and International Technology Practice Leader for the firm. David's expertise covers a vast array of public, private, and venture funded biotech companies.

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Integrating The Digital And Physical Supply Chain In Clinical Trials

JIM MURPHY

For decades, the pharmaceutical industry was characterized as risk averse, conservative, and slow to change. In such an environment, being a change agent was not often a job requirement. That's no longer the case, as innovation outside the laboratory is valued as never before. One change ready to be explored is improving the efficiency and effectiveness of the clinical supply chain by adopting a holistic model that will minimize costs, increase agility and control, and provide greater traceability.

THE BENEFITS OF A SEAMLESS DELIVERY MODEL

A holistic clinical drug supply solution combines an advanced technology platform for managing patients and supplies with the domain expertise and resources to perform end-to-end supply chain manufacturing and logistics. It enables seamless coordination of key steps — from supply planning and interactive response technology (IRT) implementation through to packaging, labeling, distribution, returns, and product destruction. It leverages real-time enrollment information and tight process integration to enable an iterative delivery model.

Adopting a holistic solution can be transformational. Although the benefits will vary from one study to the next, most companies should generally realize:

- Shorter start-up time lines, made possible by simplification of packaging design and IRT requirement definition.
- Reduced product wastage, through batch packaging and labelling operations.
- Greater adaptability to unpredictable enrollment patterns through real-time patient and drug information.
- Reduced logistics costs as a result of actively managed drug resupply strategies.
- Simplified management of mid study changes, whether the result of protocol amendments or Adaptive Designs.

Plus, the sponsor team's experience during study start-up is improved when a partner takes responsibility for setting up the digital and physical elements of the supply system. Ideally, the relationship will transcend tactical execution and deliver on strategic goals that lead to continuous improvement and value creation.

IMPEDIMENTS TO PROGRESS

Although the advantages of a holistic solution are compelling, there are several reasons why many sponsors haven't adopted a comprehensive approach:

1. Sweeping transformation of this nature often threatens the status quo for the sponsor team responsible for making outsourcing decisions. Additionally, entrusting a service provider with such significant responsibility can be unnerving for some companies.
2. Digital and physical supply chain services are typically outsourced at different times by different functions in the sponsor company, making broad scale decisions difficult.
3. Strategic outsourcing of this scope lends itself to risk-sharing arrangements, although the fact that protocols are prone to change makes it difficult to monitor and manage performance.

While these challenges may seem daunting, none are insurmountable.

A ROADMAP FOR CHANGE LEADERS

Companies interested in a holistic supply chain model can realize many benefits, but scaling up to the point where a *large portion* of a sponsor's clinical programs are handled in this manner may be a lengthy process. Many companies begin with a pilot and wait for data demonstrating measurable value before institutionalizing the approach.

Change leaders who want to drive adoption of a new supply chain model will want to:

- explain the overall vision and desired benefits to the domain experts in the company's IRT and drug supply teams
- use real-life case studies to provide proof points demonstrating the validity of the approach
- work with internal teams to identify potential pilot opportunities, which could include Phase 2 studies, investigator-initiated trials, or small trials involving biologics
- ensure executive-level sponsorship exists on both sides of the relationship in order to support alignment and aid in facilitation of change
- define key metrics for success
- collaborate with the vendor to produce a strategic plan to reduce the total number of study drug units produced and shipped
- conduct a pilot, monitor progress, and expect the vendor to provide meaningful and measurable benefits
- where appropriate, embed service provider resources into the organization to ensure smooth knowledge transfer and support effective expansion of the model.

Affecting operational change of this magnitude is never easy. Yet, with the right assistance and overall plan, it is quite achievable. In adopting a seamless delivery model across the digital and physical supply chain, change agents have a rare opportunity to transform a large and growing cost driver in drug development. L

Jim Murphy is President of Almac's Clinical Technologies Business Unit, a role he has held since 2006. He also leads Asia Pacific operations for the Almac Group, overseeing the company's strategic expansion in the region.

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You Shouldn't Have To Look Behind To See If Anyone Is Following You

JOHN BALDONI

Who will follow you? That's a question that many executives ask — or should ask — themselves regularly. The problem is that they might not like what they hear. According to research conducted by Sebastian Brion at IESE (the graduate business school of the University of Navarra), and as reported in *The Economist*, "Those primed with high power were convinced that others were on their side; a view not shared by those being bossed." In fact, at times those lowly powered "would form alliances against the powerful, even when it was not in their financial interest."

Wake up, bosses. Or better yet, you might want to sleep with one eye open.

In reality, as *The Economist* notes, few people (other than at the top) would be surprised at these findings. It is human nature to distrust those at the very top unless they demonstrate that they truly have our best interests at heart. One reason for growing rates of distrust in organizations is that employees feel that the rules of accountability do not apply to those at the top. Employees who are denied raises or merit pay are annoyed, justifiably so, at senior executives who get big bonuses even when the company does not achieve its financial targets.

So what can a boss do? Lead by engaging the hearts and minds of those you lead. As I write in my newest book, *MOXIE: The Secret to Bold and Gusty Leadership*, you need to make engagement tangible. Bosses engage best when they do the following:

SET CLEAR EXPECTATIONS.
Yes, bosses do an okay job of telling subordinates what they are supposed to do, but fewer bosses take the time to link what the employee does to the vision and mission of the organization. Clear expectations shape the employee's outlook on the work and facilitate collaboration among colleagues to think creatively and execute accordingly.

LISTEN WELL.
Busy bosses may think they have an excuse for not making time to listen, but they are kidding themselves. Listening to employees discuss their projects as well as provide ideas and suggestions for continuing the project is critical to the good running of the enterprise.

HOLD THEMSELVES ACCOUNTABLE.
Results are critical to those in management. Good bosses are those that do whatever it takes — within reason — to achieve goals. At the same time, when things fall short, they accept consequences for themselves.

PUT OTHERS FIRST.
Good bosses share the spotlight with others. They are the first to push others to receive credit for a job well done. And when things do not go well, they accept blame.

There is something else I have noticed that exceptional bosses do. They make themselves available to their employees. For example, they attend employee gatherings, and when invited, show up at an employee's family events. They also work behind the scenes to provide support to employees in need of assistance with family issues or medical challenges. In short, such bosses are there for their people.

As best-selling leadership author and inspirational speaker, John Maxwell, puts it: "A leader is one who knows the way, goes the way, and shows the way." Bosses need to earn the respect of their employees every day. Good bosses know this; mediocre bosses do not. It's as simple as that.

John Baldoni is chair of the leadership development practice of N2growth, a global leadership consultancy. John is the author of more than a dozen books, including the forthcoming *MOXIE: The Secret to Bold and Gutsy Leadership* coming this October.

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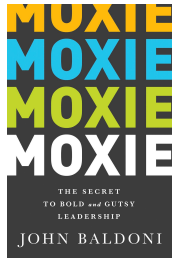

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