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"I try to move projects as quickly as possible to either signature or decline."

George Golumbeski, Ph.D.
SVP of business development, Celgene

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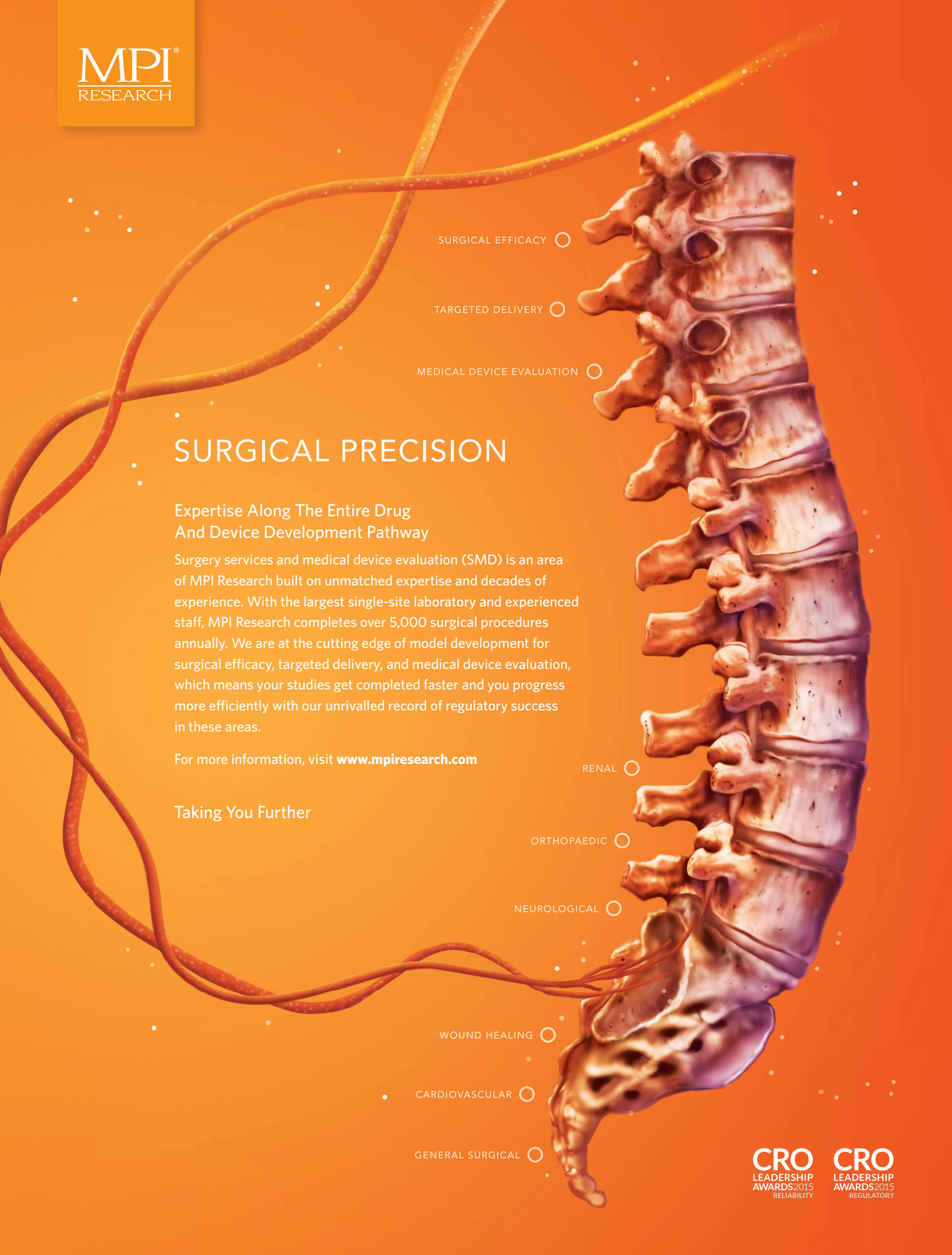

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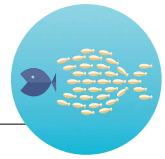

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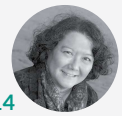
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The Importance Of Having Partners You Can Count On

ROB WRIGHT Chief Editor

June provided a significant number of educational opportunities for life science executives. If you have any interest in oncology, you could probably be found at Chicago's McCormick Place attending the American Society of Clinical Oncology's (ASCO) annual meeting (May 29 to June 2). Biopharmaceutical manufacturing experts, such as *Life Science Leader* magazine editorial advisory board member, Andrew Skibo, were busy sharing best practices and insights during the ISPE/FDA/PQRI Quality Manufacturing Conference (June 1 to 3). Two weeks later, Washington, D.C., played host to the Drug Information Association's (DIA) 51st Annual Meeting (June 14 to 18). At all of these valuable industry shows, it is likely you could find past, current, and future *Life Science Leader* editorial participants. But one person you would not have found at all three — me.

When agreeing to serve as BIO International's Program Committee co-chair with Celgene's SVP of corporate affairs and strategic market access, Richard Bagger, a conscious decision was made on how I would spend my most precious, limited, and non-renewable resource (i.e., time). Rather than try to be Jack of all tradeshows and master of none, with the annual convention also taking place in June (15 to 18), it seemed best to focus on helping plan, prepare, and execute only on BIO. (We are grateful to BIO for entrusting *Life Science Leader* with this tremendous partner responsibility.) Besides, our other editors were just as busy as I covering all of those other events.

For example, while *Life Science Leader* executive editor, Wayne Koberstein, was hard at work digging for future editorial ideas at ASCO, *BioProcess Online* chief editor, Trisha Gladd, and *Pharmaceutical Online* chief editor, Ken Congdon, gathered need-to-know regulatory insights and innovations in manufacturing systems at the Quality Manufacturing Conference. Whereas *Clinical Leader* chief editor, Ed Miseta, was diligent in discovering advances at DIA, *Outsourced Pharma* executive editor, Louis Garguilo, and Koberstein were striving to develop super powerful connections at BIO. All have contributed to the high-quality content at *Life Science Leader*. More than colleagues, they are editorial partners who can be trusted to consistently execute — flawlessly.

In fact, the intricacies of partnerships was one of the key topics discussed in this month's cover feature (see p. 16) on Celgene's George Golumbeski. He believes, when it comes to exercising control in an R&D partnership and/or an in-licensing deal, less is more. The SVP of business development is an advocate of empowerment — even going so far as to provide Celgene collaborators with final decision-making authority if consensus cannot be reached via agreed-upon partnership governance mechanisms. While Golumbeski is clear to point out that this "empowering escalation clause" exists only up to the point when Celgene opts to internalize a program, it is also clear his hands-off approach is very effective when it comes to delivering results. "If you've been very assiduous in picking your partners in the world of 'X,' why would you want to do a deal and then turn around and tell them what to do in the very early stages of whatever 'X' is," he says. It seems much can be learned from exercising self-control when it comes to wanting to meddle, especially if you want to build collaborations with partners you can count on. L

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Q How is patient access to information changing healthcare delivery?

A PATIENTS ARE INCREASINGLY DRIVING THEIR OWN TREATMENT PROGRAMS – a challenge we are not prepared to manage. Patients used to come to physicians armed with ads from *Reader's Digest* to ask for new drugs being promoted by pharma companies. Now they come armed with requests for new tests, assessments, and treatment approaches that even the academicians may not be fully aware of. Some cancer patients are already paying private labs to breed mice that will carry their tumors. Treatments can then be tested on these customized "Avatar" rodents to determine what may work best. While this trend is most visible in oncology and rare diseases, it could catch on in other therapeutic areas.

MARY ROSE KELLER
is the VP of clinical operations at Tocagen and has 30+ years of industry experience in clinical development strategy and execution of global Phase 1 to 4 clinical trials for drug, biologic, and diagnostic products.

Q What are the top trends in our industry, and what should executives be doing to capitalize?

A (1) THE RENEWED NEW PRODUCT FLOW (42 NMEs [NEW MOLECULAR ENTITIES] IN 2014); (2) THE GROWING PRICE PUSHBACK FROM PAYORS; (3) THE EMPOWERED CONSUMER. The new product flow environment is real, as $24 billion was added in new sales over a 12-month period versus the usual $2 to $5 billion. Executives need to get going with quality R&D and in-licensing work. When approached to sponsor proposals, in addition to assessing the credibility, competences, and mutuality of interest between you and the submitter, make sure the project fits your strategic and financial goals. Also, if you go through an M&A, be sure to treat people with respect, being fair in the way you design the new structure and assign jobs. Learn as much as you can, and try to have the combined company work with the best ideas and practices.

FRED HASSAN
is the managing director at Warburg Pincus and former chairman of Bausch & Lomb. He has served as the CEO of several pharmaceutical companies and chaired significant pharmaceutical industry organizations.

Q What innovations are needed to create better diagnostics in order to realize the benefits of personalized medicine?

A MORE INFORMATION ON THE IMPACT OF GENETICS and the factors that influence expression of genetic abnormalities is necessary before we can create truly personalized medicine diagnostics for any disease. Right now, we have a number of genetic markers that are implicated, but we have yet to discern whether these markers, *in all cases*, result in disease, in super responders, or in absence of disease. We can catalog genetic changes, and we can test for them, but we can't know for sure that a single genetic polymorphism will affect all people who have it in the same way. Other gene changes, known or unknown, can modify specific genetic effects, and a substantial number of genetic anomalies are modified by environmental influences. We're at the beginning. We have a way to go.

CAROL NACY, PH.D.
is CEO of Sequella, Inc., a private company that develops new anti-infective drugs. She was formerly CSO at Anergen and EVP/CSO at EntreMed. Prior to her business experience, she directed research in tropical infectious diseases at Walter Reed Army Institute of Research, Washington, D.C.

Tonix Pharmaceuticals

Restorative Sleep and a Second Pathway to Pain Control

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Tonix Pharmaceuticals has two development programs underway for one drug, TNX-102 SL (cyclobenzaprine), the first in Phase 3 for fibromyalgia; the second, Phase 2 for post-traumatic stress disorder (PTSD). Both programs aim to use an increase in "restorative sleep" as "a means to broadly improve the patient's symptoms," including pain. A third development program, with TNX-201 (dexisometheptene mucate) for episodic tension-type headache is due to launch a Phase 2 trial in June 2015.

WHAT'S AT STAKE

The pain comes from everywhere — and nowhere. It's in the air or even in empty space. It forbids all rest, all slumber.

That is the common denominator of fibromyalgia and post-traumatic stress disorder (PTSD), conditions targeted by the two Tonix development programs for TNX-102 SL. The key to treating both conditions is not to deaden the pain but to get at one of its chief sources — lack of sleep. The drug has two mechanisms — antagonism of both the serotonin type 2A and alpha-1 adrenergic receptors — for facilitating "restorative sleep" in patients. "By improving the sleep, we end up getting changes in the pain," says Dr. Seth Lederman, CEO. "Our drug is about sleep quality, not quantity. It is not an analgesic; it works by potentially improving fibromyalgia at a more fundamental level."

Results from the Phase 2b study in fibromyalgia were mixed but ultimately supportive of the company's thesis. The fall in mean daily pain scores among treated patients versus placebo (the primary endpoint) did not reach statistical significance, but a third of them reported a drop in pain of at least 30 percent (secondary endpoint) — a "clinically meaningful response." This is what mid-stage studies are for — sorting out the endpoints — and a well-designed trial will often reveal greater potential for the secondary. "We told the FDA that we believe the responder analysis is a better measure of the drug, and they agreed with our view," Lederman says.

Often in fibromyalgia, he explains, a regional chronic pain becomes generalized pain due to changes within the central nervous system over time. Someone may start with localized lower back pain, but after years of receiving the pain signal, the sensory-processing biology changes until pain seems to come from everywhere at once. He says treatment with TNX-102 SL may work to reverse those changes and bring patients back to having the original localized pain, "a normalization of the way that the brain is interpreting pain."

TNX-102 SL may have the advantage of greater tolerability, Lederman suggests, because it appears to lack the side effects of already marketed prescription pain and sleep medications. He also sees the drug as a positive alternative to the use of opiates in chronic-pain conditions such as osteoarthritis and post-surgical pain. "Unfortunately, patients with a significant fibromyalgia component are probably the ones who are resistant to opiates but also the ones whom doctors chase with higher and higher doses of opiates."

PTSD shares many traits with fibromyalgia. Thus, the company may be able to leverage the safety data from the fibromyalgia trials in its development of the PTSD indication, especially considering its military context. The small company can use every advantage it can get in this reputedly risky area, from which much larger companies have retreated.

The third development program, with TNX-201 for episodic tension-type headache (ETTH), is interesting as well. All of the approved medicines for ETTH contain a barbiturate, butalbital. In TNX-201, Tonix believes it has an analgesic that targets a novel pain-reduction mechanism, via a specific brain receptor never before a focus of drug development. The original compound, isometheptene, approved in the 1930s, was taken off the market in its old "racemic" form (mixture of two isomers) due to a lack of modernization, but Tonix is developing TNX-201 as a single isomer of the earlier compound according to current FDA standards.

DR. SETH LEDERMAN
CEO

Vital Statistics

18
Employees

Headquarters
New York

Finances

Total raised about
$110M
No VC rounds. Went public through reverse merger into shell. Forty percent institutional ownership.

Latest Updates

May 13, 2015:
Launched Phase 3 clinical study of TNX-102 SL in fibromyalgia.

Looming Cadillac Tax And ACOs **Distort Healthcare System**

JOHN McMANUS The McManus Group

By the time this article goes to press, the Supreme Court may have ruled on the constitutionality of subsidies for health insurance flowing through the federal exchange. But other distortions caused by Obamacare are rippling through the healthcare system. Two clear examples are the looming "Cadillac Tax" on generous health plans and unfolding theatrics regarding accountable care organizations (ACOs).

CADILLAC TAX TO HIT 60 PERCENT OF EMPLOYER PLANS

The so-called "Cadillac Tax"— the 40 percent excise tax on the value of health plans that exceed a threshold the architects of Obamacare find too munificent — is the latest case in point. The tax is collected on plans whose value exceed $10,200 for individual coverage or $27,500 for family coverage. As Professor Gruber, a key architect of Obamacare, gleefully explained in a famously leaked video, Democrats deliberately "mislabeled the provision as a tax on insurance plans when we all know it's a tax on people who hold those insurance plans."

Although it does not go into effect until 2018, many employers and unions are already adjusting their plan offerings in anticipation of the hefty fee impacting their multiyear contracts with employees. Business and labor are unified in seeking its repeal, and bipartisan legislation has been introduced to rescind the tax.

"Cadillac Tax is really a misnomer; potentially any employer can be hit by the tax," said Beth Umland of Mercer, a major health benefits consulting firm. Mercer predicts that by 2022 more than 60 percent of plans will be ensnared by the pernicious tax, up from just 22 percent initially.

Part of the problem is that *employee* contributions to their own healthcare through health savings accounts and flexible spending accounts are counted toward the threshold that triggers the excise tax. Why should employee healthcare savings vehicles be conflated when employers purchase health insurance that's considered too generous? The pretax employee-funded accounts have served as an important bulwark as employers have shifted more costs to employees.

The second major reason nearly two-thirds of employers will eventually be taxed for offering coverage deemed "too generous" is that the threshold is indexed to the consumer price index plus one percent, which lags behind health inflation. The CPI grew at 2 percent last year, while the Congressional Budget Office projects health inflation to rise at 5.6 percent over the decade. It should be no surprise that the 40 percent tax will raise $87 billion over the next decade and grow in importance, likely forcing employers into skimpier health plans with substantial deductibles and cost-sharing and narrow provider networks akin to the offerings in the Obamacare exchanges.

This paternalistic view that government knows best how much healthcare an individual should be provided by willing employers is reflected in the typical deductible for a family plan in the "silver" or middle-tier plan offered in the Obamacare exchanges: $6,000 in 2015 (and slated to rise by double digits next year). While the administration touts evidence of the number of uninsured falling in recent years, most newly-insured have policies with such substantial cost sharing and narrow networks of providers they're deterred from seeking routine care. A looming tax that is likely to result in many employers substantially hiking deductibles or scrapping pretax health account vehicles that assist these individuals with their out-of-pocket expenses will only exacerbate the problem.

ADMINISTRATION SUPPORT OF ACOs REGARDLESS OF RESULTS

Meanwhile, the administration is undertaking bizarre contortions to maintain interest in another key feature of Obamacare: Medicare Shared Savings Program (MSSP) ACOs — provider groups tasked with coordinating care and reducing healthcare costs. ACOs were envisioned to encourage mega-hospital systems to emulate integrated health organizations such as the Mayo Clinic and Geisinger Health System to create shared savings for the Medicare

program. But in a series of actions, the administration abandoned almost any pretense that such organizations will actually accept risk and contain costs.

When the program was first announced in 2011, CMS (Centers for Medicare and Medicaid Services) called for MSSP (Medicare Shared Savings Program) ACOs to accept two-sided risk: ACOs that contain costs below benchmark spending could share in the savings, but those whose costs exceed the benchmark must accept part of the loss, just like any capitated insurance plan, except that the government would also share in the losses.

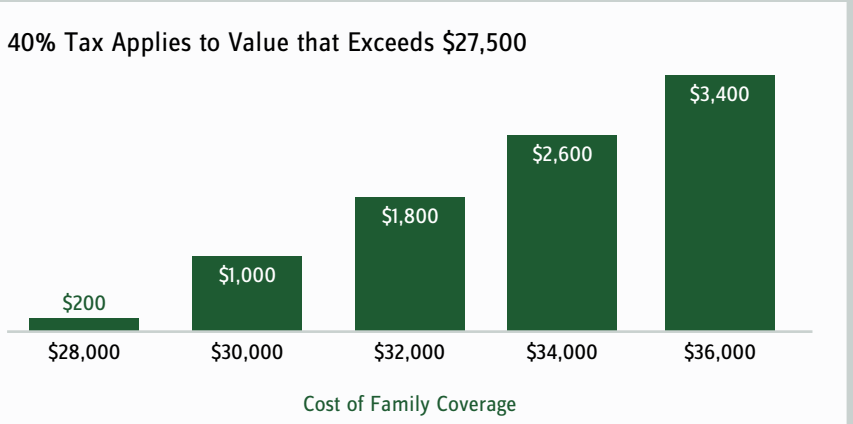
But, following stakeholder backlash and over 1,300 submitted comments, CMS caved in the final rule. Participants were provided with the option to partake in a two-sided risk model or enjoy a three-year period of risk-free participation after which ACOs would be required to share in both the savings and the risk. Just five out of 405 ACOs volunteered to participate in two-sided risk. Five! The other 400 got to play a game of "Heads, I win. Tails, you lose." In this case, "you" is the taxpayer holding the bill for providers who fail to hit their spending targets.

With the three-year window of one-sided risk about to expire, the ACOs (i.e., mostly large hospital systems) mounted a lobbying campaign to protect their risk-free scheme. In November 2014, the National Association of ACOs commissioned a survey that claimed nearly two-thirds of member ACOs would leave the program unless substantial "improvements" were made. Several weeks ago, CMS issued a rule to allow ACOs to continue with their risk-free participation for another three years. Sensing a pattern here?

In its announcement of the retreat, CMS crowed, "We are encouraged by the popularity of the Shared Savings Program, particularly the popularity of the one-sided model." How about expressing disappointment for failure to implement a program that actually saves money?

Only one-fourth of the 220 ACOs whose contracts are set to expire at the end of this year produced any shared savings, and many of the others are expected to drop out of the program. A Medicare Payment Advisory Commission analysis last fall found that ACOs had saved a whopping 0.3 percent! Jiminy. MedPAC and the health policy community have been very supportive of the ACOs, so one can only imagine the tortured computations and analysis required to show even the slightest savings.

Impact of Cadillac Tax on Family Coverage



Nonetheless, the administration has put the word out that these large health systems must be nurtured and protected over competing delivery systems, such as independent physician practices that already provide integrated care and large savings, shockingly, to patients AND the system, as they are paid far less for providing the identical services. Presumably, fewer providers mean fewer entities to control or influence. Big government likes big bureaucratic providers.

This is particularly confounding given the evidence that hospital employment of physicians results in less efficiency and higher costs. A recent *Journal of American Medical Association* study of 4.5 million patients in California found: 1) expenditures per patient were 10.3 percent higher for physician groups owned by hospitals than independent practices; and 2) expenditures were 19.8 percent higher for physician groups owned by multihospital systems.

Yet the threat of being boxed out of a delivery model that has led to vertical provider consolidation is resulting in troubling employment decisions by physicians. A recent study by Merrit Hawkins found a substantial shift toward hospital-employed physicians, with 90 percent at hospitals versus just 10 percent in independent practices. The administration's unwavering support for ACOs, despite their performance and its lack of anti-trust enforcement in the health provider sector where mega-hospitals control entire communities' healthcare, has fueled consolidation of healthcare providers.

At what point can the administration take note of empirical evidence of the result of their policies rather than hew to the ideological dogma that provided the basis for policy decisions made years ago? They won't. As Gruber points out, their game plan has been and will continue to be: Keep the charade going as long as possible, dig the hole ever deeper, and at a certain point it will be too big to dig out. 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.

Value & Pricing: Moving Past The Rhetoric

ALLAN L. SHAW

"To continue its prolific pace, the biopharma industry needs to embrace the changing healthcare system."

Today we bear witness to a "golden age" for biopharmaceuticals. With all of the exciting/innovative science, growing scripts, increase in drug approvals, and record revenue, it's difficult to call it anything else. This is all occurring as the healthcare (HC) ecosystem is embarking on unprecedented change to fundamentally reform the HC system to squeeze out excessive inefficiencies/waste before it bankrupts the system. Maintaining the industry's momentum while navigating a changing environment will be extremely difficult, particularly in the face of pressures to curtail increasing healthcare costs and the growth in spending on medicines. What does biopharma need to do to operate within the resource confines of its ecosystem to enable optimal patient access to innovative medicines while fostering alignment among stakeholders?

Healthcare's economics historically have been substantially volume-based, with very little correlation to outcomes, which contrasts with almost any other industry. Could you imagine purchasing a car if manufacturers did not stand behind its performance? Given global cost-containment initiatives, the ecosystem is evolving into a value-based system whereby accountability and outcome-based reimbursement will supersede the volume-based model currently in place (e.g., risk-sharing by NICE [National Institute for Health and Care Excellence]). For example, price controls in the rest of the world have put pressure on capturing profitability in the U.S., while the share of total branded drugs purchased by the U.S. continues to decline annually and is now approaching 30 percent. This will completely change how the game has been played; commercial success will depend on demonstrating a product's "value proposition" based on clinical and economic evidence. Clinical evidence will need to encompass head-to-head comparisons with the "standard of care" to demonstrate value-differentiation and provide better labels. This new reality will reward truly innovative medicines in noncompetitive categories while facilitating the extinction of "me-too" branded products. Of course, in many disease states, both of these issues are being addressed simultaneously, as novel drugs are being tested in second-line combination therapy with an inexpensive generic agent as first-line therapy. A secondary benefit of this paradigm is that all patients are given active treatment. For example, in the lucrative type 2 diabetes market, an experimental drug versus placebo is often being tested in combination with metformin, which is provided to all patients in the clinical trial.

Ideally, a value-based system will provide a framework to rationalize pricing and optimize resource allocation. With that said, the devil is in the details. What is value, and how do you prove it? There are many factors to be considered, including disease and patient management. In my opinion, a drug's value is determined by its comparative effectiveness to the standard of care. Underscoring this point, Europe has been practicing referencing pricing and requiring "standard of care" comparator arms in clinical studies for many years. Determining "cost-effectiveness" (e.g., evaluating both pricing and efficacy versus standard of care at appropriate doses with sufficient sample size, double-blind trials, etc.) will be critical in allocating limited healthcare resources. While it may be "more art than science," I offer the following thoughts concerning establishing the value proposition:

- Need to evaluate the cost-effectiveness of an innovative therapy versus the standard of care.
  - Generate and capture data to render a more cogent decision regarding pricing.
- Do the clinical results provide empiric estimates of relative efficacy and safety as compared to the standard of care?

- Create a strategy for developing the value proposition for new drugs, including price-sensitivity estimates, and for identifying the appropriate health economic endpoints that should be included in Phase 3 and even Phase 2 trials to allow pharmacoeconomic modeling to optimize commercial outcomes.

- Outcome data is critical for demonstrating and maximizing a product's commercial value while facilitating patient access. For example, in the absence of overall survival benefit, the combination of progression-free survival and health-related quality-of-life outcomes versus the standard of care in a well-designed trial is likely to lead to positive evaluations from regulators and payers.

While the pace of change at times is akin to watching Muhammad Ali use his "rope-a-dope" strategy to wear down his opponents, changing the way business is conducted is inevitable and well under way. The recent Sovaldi debate over the treatment of hepatitis C underscores this. It revealed the significant lack of alignment with our managed care reimbursement criteria and their correlation to outcomes (Pharmacy Benefit Managers' [PBMs'] emphasis on minimizing current-period costs over HC system costs). The Sovaldi debate highlighted the need for further systemic evolution to produce alignment (and common risk pool), particularly in the case of outcomes that have 20-year horizons. This situation also highlighted the PBMs' emerging purchasing power given recent consolidation in the space. The payer market is no longer fragmented, as three PBMs will soon control approximately more than 70 percent of the commercial market given recent consolidation, along with Medicare part D dominating its market segment. While we are still far from a single payer system, the PBMs are currently defining the debate. This was illustrated by Solvadi decreasing in price by nearly 50 percent since losing its monopoly in this market, giving rise to many strategic/commercial questions on how to maximize contracted prices. Examples of the PBMs' enhanced negotiating power are evidenced by the increasing prevalence in restricted formularies and coupons, representing a fundamental shift in market access to contain costs. As launch preparations are being made for PCSK9, a monoclonal antibody that will be prescribed in combination with generic statin drugs to lower cholesterol and to potentially lower coronary risk, it will be interesting to see if any lessons were learned.

CHANGE IS INEVITABLE

As pricing headwinds continue to swirl, the disparity in gross-to-net pricing has never been greater, and the increasing prevalence of combination therapies of branded drugs does not help the situation, particularly in a capitated pricing/bundled environment. Given that fundamental change is inevitable, isn't it better for biopharma to have a seat at the table than be on the menu? If we don't instigate change, the shifting regulatory, public, and political environments will, and those terms will be far less favorable to the biopharma industry.

To continue its prolific pace, the biopharma industry needs to embrace the changing healthcare system. We need to do a better job of defining value and determining pricing that does not bankrupt the system. Particularly given the macro dynamics, we are approaching a breaking point that will require "commercial innovation" that generates new engagement strategies to maintain/increase patient access, along with emphasis on cost-effectiveness. There needs to be a better understanding of the market dynamics that reflect the competitive landscape and patients' needs that correlate to the industry's resource allocation and will better inform and optimize drug development activities.

The focus needs to be patient-centric: putting overall health and outcomes at the core of every decision, shifting the emphasis to value as opposed to costs and profits. Branded manufacturers need to proactively take a lead in such discussions to better define the debate to positively influence the outcome. Good, truly innovative science that addresses unmet medical needs or provides outcomes that are better than the standard of care will continue to be reimbursed reflective of their value to patients/outcomes. But branded drugs that are not adequately differentiated will be denied access. The strategy of creating the successful health ecosystem of the future starts with the right intent. Successful commercial innovation requires doing what is best for the patient and putting the patient at the center by improving health and outcomes and decreasing costs. Medicare is leading the charge from fee-for-service to innovative models based on improved HC outcomes at lower prices. These changes may prompt us to consider the following:

- We may determine that our business isn't only about drugs.
- We may need to re-evaluate our pricing models.
- We may need to restructure our business.
- We may consider extending branded exclusivity to enhance patient access and ensure adequate returns.
- We may have to reevaluate how we do our research and what should be considered as clinical evidence.
- We may consider reassessing the molecules we study and the science that we pursue. L

ALLAN L. SHAW is currently a member of Celsus Therapeutics' board of directors and serves as chairman of the audit committee. He was recently managing director – life science practice leader for Alvarez & Marsal's Healthcare Industry Group, and formerly CFO of Serono, possessing more than 20 years of corporate governance and executive/financial management experience.

Outsourcing Increasing To CROs And CMOs Known For Quality And Cost-Effectiveness

With cost and regulatory pressures on drug manufacturers continuing to increase, it is not surprising that growth of the global CRO and CMO markets is healthy (9 percent and 6.4 percent CAGR, respectively). According to market research firm TechNavio, today's greater demand for CRO services is due in large part to the increase in outsourcing of biopharmaceutical drugs and R&D activities by both pharmaceutical and biopharmaceutical companies.

NIGEL WALKER
Managing Director
at That's Nice

"It is interesting to note that large and emerging biotech companies are now outsourcing nearly as frequently as Big Pharma and generally more often than emerging pharma at the discovery, preclinical, and Phase 1 stages of drug development."

Meanwhile, Mordor Intelligence predicts that the value of the global CMO market will increase from $58 billion in 2014 to $84 billion in 2020, with APIs accounting for the largest share. Formulated products, however, will grow at the fastest rate due to pharma and biopharma companies focusing on the discovery and development of new drugs rather than on manufacturing.

The trends noted in these market research reports are in line with the results obtained from Nice Insight's annual *Pharmaceutical and Biotechnology Outsourcing* survey of more than 2,300 outsourcing-facing pharmaceutical and biotechnology executives. The survey respondents' changes in spending on CMO/CRO services clearly reflect the market growth discussed above. While the percentage of survey participants whose companies spend more than $50 million on outsourcing has remained fairly stable over the last three years at 23 to 24 percent, the percentage of respondents whose companies spend $10 million to $50 million on outsourcing has increased dramatically from 38 percent to 62 percent, while the percentage of participants whose companies spend less than $10 million has decreased by slightly more than half. Furthermore, regardless of the buyer group or budget size, the average number of services outsourced by survey participant companies increased from 2014 to 2015.

Similarly, the survey results reflect the growing importance of biopharmaceuticals to the overall drug industry. The percentage of survey participants whose companies are engaged in the development of biologics has increased from 65 percent in 2013 to 82 percent in 2015. In addition, the percentage of outsourcing budgets spent on biologics vs. small molecule therapeutics has risen from 54 to 58 percent over the same period.

The average number of services used by survey respondents also has increased the most for biotech (4.9 to 8.2), emerging biotech (5.4 to 9), and Big Pharma (5.7 to 8.8) companies, with emerging biotech and Big Pharma firms using the greatest number of services.

Those services are used during all phases of the drug development process, with the largest percentage of respondents (60 percent) relying on CROs and CMOs during the preclinical phase, followed by phase I (56 percent), discovery (49 percent), Phase 2 (42 percent), Phase 3 (29 percent), and Phase 4/post-launch (22 percent). Of course, the lower values for later stages of drug development can in large part be attributed to the fact that vastly fewer candidates make it that far

through the process.

It is interesting to note that large and emerging biotech companies are now outsourcing nearly as frequently as Big Pharma and generally more often than emerging pharma at the discovery, preclinical, and Phase 1 stages of drug development.

According to the Nice Insight survey, the top services respondents expect to outsource in the coming 18 months include clinical research, analytical services, biomanufacturing, biostatistics, packaging, and data management.

When choosing which CRO or CMO to spend their money on for these services, 67 percent indicated they rely on industry research. Consultants (59 percent) and referrals (54 percent) were the next most popular methods used to select outsourcing partners. In addition, to ensure quality, sponsors are using more methods to identify new partners, with the average number of sources increasing from 2.5 in 2013 to 3.0 in 2015.

KEY ATTRIBUTES OF OUTSOURCING PARTNERS

CROs and CMOs should take note that for the third year in a row, quality and reliability remain the number one and number two priorities for sponsors when they are looking for outsourcing partners. Productivity is also an important attribute and has steadily moved up in the rankings from fifth to third place from 2013 to 2015, likely reflecting the need for pharma and biotech companies to increase efficiencies and lower costs across all activities. In addition, when selecting CROs and CMOs, survey participants indicated that sponsors are looking for service providers that have a track record of success and financial stability. Nearly as important are operational, methodological, and therapeutic experience and the ability to be adaptable and flexible in order to meet project needs.

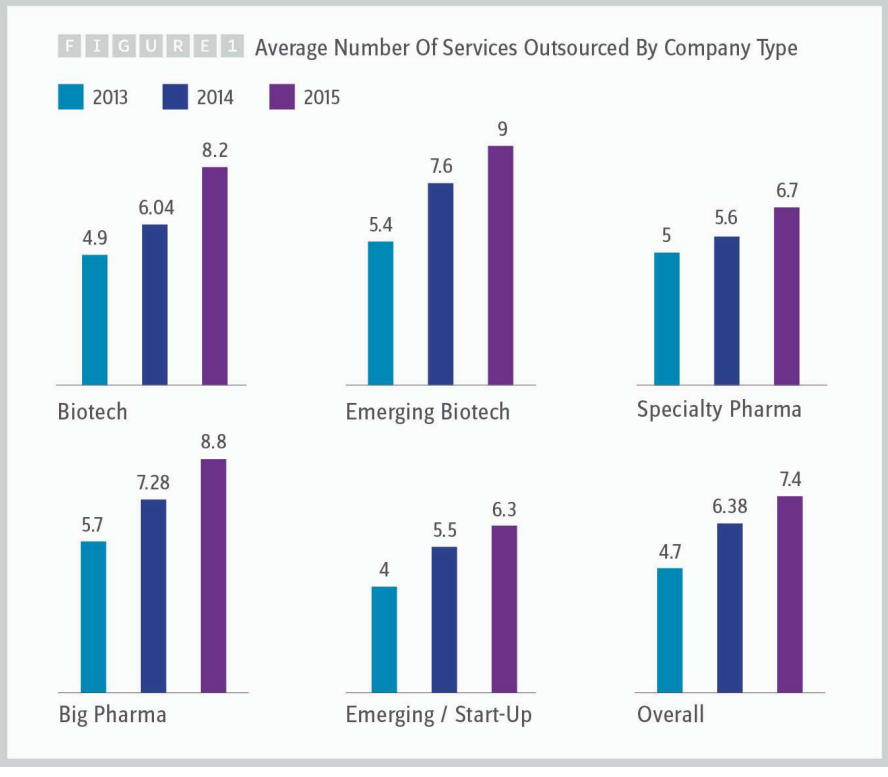
When it comes to soft traits, respondents to the survey prefer CROs and CMOs that have demonstrated good communication and transparency when doing business, combined with an industry reputation for doing quality work and understanding the needs of their customers. Service providers that are also known to be responsive, willing to go the extra mile to ensure success, able to implement sponsor methodologies, and eager to foster good rapport among the members of their project teams will also receive extra attention according to survey participants.

For CROs and CMOs that want to establish strategic partnerships with their customers (79 percent of whom are either interested or very interested in forming strategic partnerships with their service providers), having the capability and willingness to collaboratively develop operating procedures should be a top priority, according to survey participants (in both 2014 and 2015). The use of dedicated project managers, clear interest in making long-term commitments, and the ability to customize protocols for different projects are also important in successful strategic partnerships.

It's not surprising that quality is the top performance metric for respondents to the survey. However, the second most-sought-after performance metric — cost-effectiveness — is a bit surprising given that when it comes to selecting CMOs and CROs, affordability is the fourth most important priority for survey respondents.

Poor quality continues to be the top source of dissatisfaction for survey respondents, followed by a lack of timeliness in resolving problems and unexpected charges. The latter is again surprising given the lack of emphasis on cost when selecting CROs and CMOs, but it does fit with the fact that survey respondents consider cost-effectiveness a key performance attribute.

Clearly, the survey results indicate that CRO and CMO use is increasing and that those service providers with proven expertise and a demonstrated ability to deliver high-quality materials on time and cost-effectively will have the greatest opportunity to leverage that trend for increased success.



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. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~125 CMOs and ~75 CROs servicing the drug development cycle. Five levels of awareness, from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. 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.

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

CELGENE: MASTERING PARTNERING & M&As TO BUILD ITS NEXT GENERATION OF ASSETS

By R. Wright

GEORGE GOLUMBESKI, PH.D.
SVP of Business Development, Celgene

CELGENE:

Mastering Partnering & M&As To Build Its Next Generation Of Assets

ROB WRIGHT Chief Editor @RfwrightLSL

"Twenty five years ago, if someone had said to me that I'd go on to do good work in business development, my response would have been, 'What's business development?'" jokes George Golumbeski who has a Ph.D. in genetics and did his post-doc work in molecular biology. But today he is SVP of business development for Celgene and is often considered the biopharmaceutical grand master of how industry deal making should be done.

For instance, he recently helped ink a deal for his employer to acquire Quanticel Pharmaceuticals for an up-front payment of $100 million in cash and up to an additional $385 million in contingent payments. Golumbeski recently shared with me his approach to assessing and developing the deals that are designed to build Celgene's next generation of pipeline assets.

The Path Of The Deal

Since his arrival in March 2009, Celgene has executed more licensing deals than any other biotech (e.g., 10 in 2014). When asked for a step-by-step approach as to how he assesses a potential deal, he says it begins, simply, with focus. "Celgene is an oncology and a chronic inflammation/autoimmune company," he states. "We have just those two therapeutic areas, and we look at everything from pre-clinical, early-stage science and molecules all the way up to large M&As in that space."

From there he says the process includes incoming nonconfidential disclosures, which typically include data embedded in a corporate PowerPoint presentation. This information is then reviewed by a group of people from various disciplines. Depending upon the asset's stage of development, the review team might include someone from clinical, research, commercial, and regulatory. Once through a first pass, if the deal looks interesting, the decision is made to sign a confidentiality agreement, which is almost invariably followed by an in-person meeting. "It is rare for these meetings to be conducted over the phone or via a webcast," he

attests. The first meeting is usually a two- to three-hour 360-degree view of the program. "We look at top-line scientific data, clinical data, manufacturing issues, intellectual property, and future development plans," he explains. "We meet the team, and after lengthy discussions, decide either to pass on the opportunity or progress to a full and thorough due-diligence step." If all goes well during that step, the process moves forward to a financial proposal and a legally binding contract.

How To Assess A Potential Deal

When I ask him what he looks for in a deal, he says, "You know it when you see it." Although, he adds that, regardless of the stage of development the company is in, he and his team are looking for the potential for *quantum* steps forward, not small, incremental advancements.

When first assessing a potential deal, Golumbeski says Celgene applies a staged approach. "If we're talking pre-clinical programs, it is incredibly important to know the molecular target of the therapeutic agent you are working on," he states. "If that is a known gene product which drives the transformation of cells from benign to malignant, then that's positive." The second thing that's really important at the pre-clinical stage is safety and efficacy data. "If we're talking oncology or inflammation, there are pre-clinical animal models for all of this work." Known as xenograft studies, in cancer these involve implanting human tumor cells into a mouse, letting the tumor grow, and then testing the drug for efficacy. According to Golumbeski, while everybody wants to see well-done, carefully controlled xenograft data for cancer drugs, he explains that these models can be erratic in their predictability. When looking at these studies, Golumbeski's team is not only reviewing data, the biology associated with the target, and the case the sponsor makes for safety and efficacy, but also the quality of the argument and the rigor of the sponsor's thinking. "You can see almost comparable data," he says. "But it is clear that some teams have thought their work through and know where their data is strong and where it's not fully fleshed out, versus others who lack the same degree of critical thinking."

When it comes to assessing a therapeutic that is already in the clinic, while the previously mentioned criteria remain important (i.e., molecular target, animal efficacy modeling, and quality of thinking), these are trumped by a significant corpus of human data. "The further up the drug development food chain you go, the more true this is," Golumbeski attests. "Efficacy data in Phases 1 and 2 trumps pre-clinical data. If you have a completed Phase 3 package and the drug is on the market, you really start to focus on the established profile of the drug and a rigorous sales forecast/financial model."

Indeed, no matter what clinical phase the company is in, it is very possible — and important — to make financial projections as to what the product might do commercially. "Once we have proof-of-concept data, commercial and financial projections become two of the top three to five things we look at," he explains. Though Golumbeski has seen potential partners make reasonable commercial forecasts, he also has been witness to ones that are overly optimistic. "How accurate or inaccurate those forecasts are doesn't drive our decision, because, in the end, we are going to look at our forecast," he explains. "When you're talking about an M&A of a company with an on-market drug, most acquirers have very

Do You Empower Your Employees To Challenge You?

A little over two years ago, there was a nonconfidential summary being circulated throughout the Celgene business development (BD) team about some work being done by VentiRx Pharmaceuticals. "I had looked at this, and based on some history with Toll-like receptor compounds, I just said, 'No, this mechanism makes no sense,'" George Golumbeski, SVP of business development at Celgene recalls. "Today this is now a super-hot area, broadly defined as immuno-oncology." So why did Celgene end up putting together a $35 million deal with an option to buy VentiRx? Dr. Kristen Hege, a member of Celgene's Phase 1 translational medicine unit, who has worked in cancer immunotherapy for a long time, thought Golumbeski and Celgene's head of R&D, Tom Daniel, M.D., were not giving the opportunity adequate consideration. Hege convinced Golumbeski and Daniel to sit through a presentation by the president and CEO of VentiRx, Robert Hershberg, M.D., Ph.D. "He took us through a whole series of pre-clinical and clinical experiments that really turned the tide with respect to our collective thinking," Golumbeski says. Though he initially attended the meeting out of respect for Hege, the presentation helped educate the Celgene team on an opportunity, albeit relatively risky, that had significant merit. "So, we funded a pretty significant program with an option to buy at the end of Phase 2," he states.

According to Golumbeski, anyone who thinks that getting a meeting with the head of a company's BD department is the key to a deal should, instead, focus on having good data. "I get a number of requests for meetings just to introduce the potential partner and its non-confidential data," he says. "My response is almost always, 'no' or 'not until we have reviewed the data.' The reason the meeting with VentiRx worked was that, admittedly, I had not spent enough time reviewing the data, which was really good. Weak data, whether in PowerPoint or presented in person, is going to produce a negative outcome." Another takeaway is to make sure your people, like Kristen Hege, feel empowered to challenge you.

sophisticated financial models. When you are offering 'X' up front, and the partner thinks it should be 2X, the key isn't that there is a gap but figuring out ways *to bridge* the gap." If Golumbeski's team thinks the data and the employees of the company being acquired are really exceptional, an over-the-top forecast alone will not induce Celgene to walk away from the deal. "You need to get into a discussion with your potential deal partner, so you can find out if they really believe their forecast, as well as if they are flexible in trying to bridge any differences we identify," he says. For example, Golumbeski recalls a situation in which the Celgene BD team had a long, protracted disconnect with a potential partner on valuation. "We tried hard for about a year to work out a financial arrangement that could be the basis of a deal," he recollects. Unfortunately, this company had a structure in mind that was driven by extremely high expectations. Despite Celgene's best efforts, the two weren't able to get a deal done. However, it has been his experience that these types of situations are usually able to be resolved.

Having killed a few deals throughout his career, Golumbeski estimates less than 5 percent of the time this happens as a result of unreasonableness about financial parameters. Deals are more often derailed by the quality of the data not meeting Celgene's scientific goal for a nonincremental medication. "We don't always have to be first in class," says Golumbeski. "But if we're not first, we certainly want to be best-in-class, and we're really not interested in being third, fourth, or fifth in class."

The Wisdom Of Teams Versus Committees

Since joining Celgene, Golumbeski feels there has been a pretty consistent process for bringing deals forward — continuous communication and small teams. "When we went to buy Abraxis BioScience [a deal valued at $2.9 billion], the key "deal owners" were myself, a BD colleague, a very senior clinician who reviewed all the data, Mark Alles [president and COO], and the head of the commercial oncology business [at the time] who made the case," he explains. As to whom they were making the case, Golumbeski says, "At Celgene it involves the people you would expect: the CEO, Bob Hugin; the CFO; the head of the oncology business; the head of the inflammation business; the head of business development; the head of R&D; and the corporate counsel." This group meets every one to two weeks. As a result, senior leadership has a clear understanding of what is happening as a deal is being built. "When we think we have acceptable terms, and it's time to get approval from our board, the conversation is very

Why Deals Require Champions

Business development textbooks would probably tell you that BD people really can't or shouldn't champion deals, because if they become too attached and the deal stalls or is determined not to be a fit, they may have trouble killing it. While Celgene's SVP of business development understands why this seems rational, George Golumbeski thinks that, regardless of the BD model you employ, it is important for your BD folks to champion deals — at least up to a certain point. "If they were doing a painting," he analogizes, "they have to take the painting to the point where somebody can begin to see what it is." Whether a deal has to be painted a third, half, or three quarters of the way depends on the deal and the competency of your team. But Golumbeski reminds, "Unless somebody from the appropriate function champions the deal as a lead or serves as a co-champion, it is likely to remain unfinished."

In Golumbeski's lengthy tenure, it is not the norm for championship of a deal to start with someone at the highest levels within an organization (e.g., head of R&D or a head of commercial). As a result, he is a big advocate of taking ownership. "One thing I coach my team on is not just the importance of being tenacious in getting a deal done, but also to know when to pull the plug," he says. "You have to be like an ER physician when it comes to triaging which deals to champion and which deals are better off for both parties to be let go." Like ER physicians, Golumbeski wants his BD people to be champions on one hand, yet compassionate on the other, and not to become distraught and dysfunctional when having to walk away.

Although he believes good BD people have to be painters and physicians, he also feels that being real champions requires a thoroughbred approach. "Somebody once told me that there are two kinds of horses, those you have to kick and those you have to pull back," he says. Champion BD folk, like thoroughbreds, want to run fast and get things done. "In business development, I'd much rather have people that I have to rein in once in awhile than kick," he concludes.

collegial because of the ongoing dialogue," he states.

Golumbeski views this process as being more efficient than the formalized committee review, primarily because everyone has bought into Celgene's pipeline-building approach. "When you have a formal committee, it's a different dynamic," he attests. "One person raises a significant issue, such as the deal being too risky, and the committee can go negative rapidly." In his view, one of the primary reasons such situations take place in committees is the lack of deal familiarity. "When a committee members' sum total of familiarity is what they read in a memo or a PowerPoint briefing just prior to walking into the meeting, it is much easier to say 'no,'" he says. (For more on Golumbeski's personal experience with this, be sure to check out the sidebar, "Do You Empower Your Employees To Challenge You?")

Golumbeski prefers a "lean and scrappy" staffing model for the business development and alliance management team (Celgene's consists of 14 professional staff). Not only does this foster more of a smaller biotech culture, it avoids that traditional approach of bifurcating the deal business to people who prospect for opportunities and conduct the due diligence, and people who conduct the final negotiations. "I prefer a structure in which people run a deal from A to Z and are responsible for evaluation, due diligence, and ultimate negotiation of the financial agreement." Last, but not least, Golumbeski prefers small teams because he thinks they help promote focus. "As a company, we don't want to be looking at 300 (M&A, partnering) opportunities," he explains. "I try to move projects as quickly as possible to either signature or decline, and I think a small group helps achieve that."

The Power Of Flexibility And Empowerment

When Golumbeski embarks on a deal, he applies a few basic principles. First, he wants everyone involved to have a deep understanding of standard deal structures. Second, he suggests "to really listen to what the other side is saying, and if you can give them what they want, then give it to them." In other words, be flexible when crafting a deal. For example, when Celgene bought Abraxis, it started out as a fairly typical acquisition of a publicly traded company. "The company had a market cap, and we negotiated how much over that we would have to pay," he recollects. "In addition, the drug was sitting with a possible lung cancer approval in the relatively near term and a possible pancreatic cancer approval in the medium term." The team created a purchase price and contingent value rights (CVRs) based on Abraxis' lead compound, Abraxane, receiving approval for lung cancer. "We made another CVR based on Abraxane's approval with a certain label claim in pancreatic cancer," he says. "These got us and the seller close to a deal." However, Golumbeski recalls there being a difference between the two sides regarding the ultimate peak sales of Abraxane. "So we worked toward a number that was somewhere in the middle in order to bridge the gap and eventually agreed that if sales exceeded that number we would pay a royalty on the sales above that threshold," he states. "What really made this deal unique was it was one of the first times that CVRs had been put on the acquisition of a public company, and those CVRs were tradable on the stock market under the ticker CELGZ."

Another example of being flexible involves Celgene's recent deal with Quanticel Pharmaceuticals. The founders of the company, two Stanford professors, Dr. Mike Clarke and Dr. Steve Quake, along with the investors who had seeded

You Get What You Pay For

According to a March 2015 Bloomberg Report, Celgene paid $152 million more to partners than the industry average. When I sat to talk with George Golumbeski, Celgene's SVP of business development, I asked him the rationale behind such an approach. "I did look at that report and won't dispute what it said. But remember, almost exactly a year ago we paid $710 million up front for our collaboration with Nogra Pharma for GED-0301, which had completed Phase 2 for the treatment of moderate-to-severe Crohn's disease." The data, which Golumbeski describes as being remarkable, have now been published in *The New England Journal of Medicine*. "We would not have gotten to that $710 million number if the data had not been compelling and if the deal had not been frighteningly competitive. I don't know what period Bloomberg averaged, but if you understand how to compute an average, and you've got one or two points in there that are large, you're going to drive that average up."

That being said, Golumbeski believes Celgene does things a little differently when it comes to deals. "We've selected incredibly high-quality partners, and you get what you pay for. If you look at our deal structures versus a lot of the other companies', I think you would see that the norm in the industry is to pay a certain amount up front and then to pay a series of milestones as you go. We would rather give the company a larger amount of money up front and not pay as many near term milestones." He says this is consistent with Celgene's goal of empowering the companies it collaborates with, as well as providing them the security they are looking for from a long-term partnership. "I think one thing that has been very helpful to our success is that we have four people at the senior VP level and higher who have actually been CEOs of small, venture-backed companies, including our head of R&D and my close partner in all of our 'deal success,' Tom Daniel, and myself," he shares. "If you are familiar with running a small company, you are usually funded adequately, but you are not funded with an overage. This is the norm, but it does not always allow for the unanticipated bad news or good news, either of which can take more time and money to work through." As many of the early-stage deals being signed by Celgene range from three to eight years, their partnering philosophy is not only to empower, but also to provide adequate time to prove the science, along with the sufficient capital to fund success. In addition, Golumbeski believes funding should be enough to cover some of the inevitable "left turns" in the road companies pursuing new science often encounter.

Quanticel, Versant Ventures, all had a certain view of what they wanted the collaboration and capital structure to look like. "The only way this could be accommodated was to go through an option to acquire structure (aka 'build to buy')," Golumbeski explains. Celgene agreed to put substantial operating capital into the company (i.e., $45 million initially) and let Quanticel work for three and a half years on its technology. "Then, as we always do, we built an extension, because we never want to be at the end of the option period and have the science trending in the right direction but not have clarity on whether we should or shouldn't buy a company," he states.

Beyond the flexibility of a deal, Golumbeski has become quite a fan of what he refers to as an "empowering escalation clause." "The fundamental issue which underpins almost every non-M&A agreement between two companies, such as R&D collaborations and in-licensing deals, involves the 'C' word — control," he attests. "Every agreement typically says something like, 'The two parties will attempt to reach agreement via a joint project or steering committee.'" He says all companies have various governance mechanisms for escalating and resolving disagreements. However, most default that if consensus can't be reached, the company paying the bills has final say. "At Celgene, we will do everything we can to reach agreement," he says. "If consensus isn't reached, until that point in time where we have opted to internalize the program, we give the partner company final decision-making authority."

You may wonder how this became a standard practice at Celgene. Golumbeski says the first time the company did it there were two drivers. "Philosophically, we wanted to partner in an overly collaborative and empowering way. And, there were specific accounting rules that make a difference for how payments can be attributed. Giving final control to the other party helped us get an accounting treatment we preferred." But having done it once, Golumbeski says there was no turning back. "This was such an empowerment of our partners that, I can tell you today, whether we got the right accounting treatment or not, we would land on this idea." He says that most of the partners comment openly that they feel they are not only at the steering wheel, but also really driving the collaboration. "If you've been very assiduous in picking your partners in the world of 'technology X,' why would you want to do a deal and then turn around and tell them what to do in the very early stages of whatever 'X' is?" he says. While Golumbeski believes this approach to be a fundamental difference and something that has helped Celgene build goodwill with its partners, it isn't the main driver behind the company's partnering success. "I believe it's a strong indicator that we're willing to take a team that we think is scientifically great and managerially very strong and trust them to be the experts we perceive them to be and drive the program forward," he shares. "I believe that our thinking on this has been correct, considering that in the six plus years we have been taking this approach at Celgene, not once has the collaborating company had to exercise this clause." L

NEIL STAHL
SVP of Research and Development Sciences at Regeneron

REGENERON: COMMERCIAL CONFIDENCE FROM THE FIRST COMPOUND

LOUIS GARGUILO Executive Editor @Louis_Garguilo

In 2001, members of a small biotech from the New York City area traveled to the state capital, Albany, to discuss accessing the state's new Biotechnology Industry Growth Fund. An economic development official responsible for a portion of that fund met with them but came away skeptical.

Biotech was still a new industry; this company had failed in the clinic and was just getting new compounds into development. Its self-assuredness seemed misplaced. "When would NY residents see any return on investment?" asked the stern official. "How many jobs will your start-up create?"

I was that (myopic) state official, and let's just say I'm thankful for having gained somewhat better instincts over the years. That company, Regeneron, would go on to become one of the most successful biotechnology companies in the world, let alone in New York, where it has created thousands of jobs (see accompanying article on NY). More importantly, Regeneron has provided relief to millions suffering from disease. And further relief is on the way, with potentially three new drug approvals coming soon, more compounds in the clinic, and a pipeline that any biotech or pharmaceutical company would envy.

Constant through Regeneron's remarkable trajectory has been an outsized assuredness of success, starting from its formation in 1988. How confident has Regeneron been? Well, how many biotechs do you know that purchase a commercial manufacturing facility to control its own production *before they have a compound in Phase 2*?

Neil Stahl, SVP of research and development sciences and a 24-year veteran of Regeneron, recently told me that level of confidence flows through every scientific decision Regeneron has made and drives the company's impressive pursuit of medicines into new therapeutic areas. Below he shares more of the story behind Regeneron's success and tells us why the best is yet to come.

ONE OF THESE DAYS , A COMPOUND WILL SURELY SUCCEED

"We believed from day one we would be one of the most successful science and medicine creating organizations in the world," says Stahl, mentioning the resolve of founder Leonard S. Schleifer, M.D., Ph.D. president, and CEO; and founding scientist, CSO George D. Yancopoulos, M.D., Ph.D. "Well, maybe George didn't fully agree. He's always thought we would be *the* best."

That confidence got a boost from the outside when in 1995 renowned scientist and chairman and CEO of Merck & Co., P. Roy Vagelos, upon his retiring from Merck, decided to join Regeneron as chairman of the board. Stahl recalls Vagelos saying at the time he was impressed with the science and energy, and that given the time and money, Regeneron would lead biotech in making important contributions to science and medicine.

Stahl, for his part, had to be force-fed the Kool-Aid to get his initial confidence boost. "I was teaching at UCSF and looking around for academic opportunities," he says. "I had no idea about biotech, and certainly not in New York, when Len invited me to their labs in Tarrytown. I found this small operation, and my first thought was, 'No way in hell I would come work here.'" Stahl says that at the time there were only two biotechs that most people had heard of, Genentech and Amgen. Nonetheless, an intense, three-hour discussion of science and what a biotech could accomplish with Yancopoulos was enough to change his mind.

"People told me I was throwing my career away," recalls Stahl, "but at Regeneron I could see the science came first. We've

always taken the realistic perspective of how long science takes and for that knowledge to develop and make an impact. We planned the company's finances to ensure there is always a substantial amount of research going on. We had confidence that if the first compounds didn't work, one of these days one of them was going to be effective."

Here's what that confidence has produced so far: 2008 FDA approval of Arcalyst (Rilonacept) for the treatment of a rare genetic disease; 2011 to 2014 FDA approvals of Eylea (Aflibercept) Injection, Eylea for Macular Edema Following Central Retinal Vein Occlusion, and Eylea Injection for the treatment of diabetic macular edema (DME). Net product sales in the first quarter of 2015 were $545 million, compared to $362 million in the first quarter of 2014, and total revenue increased by 39 percent to $870 million.

Perhaps the most important results—and biggest payoff—from Regeneron's unbridled confidence to "lead with the science" is in how it has put irons in the fires of an expanding group of therapeutic arenas.

REGENERON A NEW YORK EXCEPTION ... FOR NOW

Most everyone knows Frank Sinatra's ode to New York: "If I can make it there, I'll make it anywhere… ." For the biotechnology industry, though, New York has not been the benchmark, despite respected institutions of higher learning, medical research centers, an active biotechnology industry association, and plenty of funding opportunities.

"Our two founders and executive leaders, Len Schleifer and George Yancopoulos, were born and raised and started Regeneron in New York City," says Neil Stahl, SVP of research and development sciences, who himself makes the city his home. "It's frustrating to us that although there is all this scientific talent and great universities, the New York City area is not a bigger hotbed of biotech. We're dedicated to changing that."

The scientific talent Stahl mentions resides at places such Cedars-Sinai Medical Center, Columbia University, and New York University (NYU), all ranked by the NIH as leading biomedical research institutes.

Regeneron has collaborations and stays involved with all the universities in the city. "I'm particularly affiliated with NYU and CUNY [City University of New York]," says Stahl. He considers it a company – and personal – mission to visit these universities to tell student researchers about the satisfaction and opportunities of working in the bio industry. "We open their eyes about how we do the science and the possibilities of what they can accomplish when working in large scientific groups," explains Stahl. "They learn about the resources available and the difference you make in people's lives doing research and development directly on programs that can lead to medicines. I convince them of this satisfying way to spend their intellectual energy."

But there's also the need for the entrepreneurial side as well; science and enthusiasm have to transfer to start-ups to grow a biotech cluster. In this and other measurements, New York has consistently ranked below San Francisco, Boston/Cambridge, San Diego, and Maryland/Washington, D.C., and among a second tier of clusters, including Raleigh-Durham and Seattle, for example. Momentum remains relatively strong in all these other clusters; critical mass has been achieved, and close-knit but broadening networks and infrastructure continue to be built.

New York is experiencing this growth as well. The broadening is recognized in recent surveys of biotech clusters. For example, *Genetic Engineering & Biotechnology News (GEN)* recently changed its listing for the metropolitan area from "New York" to "New York/New Jersey," which propels the cluster to third place from fifth, now behind only San Francisco and Boston/Cambridge and ahead of San Diego. This broader measurement presents the cluster as the nation's largest geographic region. It also helps mitigate what has always been considered – whether in reality or perception – a concern for bio entrepreneurs in New York: affordable and available lab space. According to GEN, the Empire State/Garden State tandem is now tops in lab space among clusters. We'll have to keep an ear to the ground on the pricing of all those labs.

Moving up to the third largest biotechnology cluster in the U.S. would be quite satisfying for most any city, but hey, this is New York! There are no likable numbers after one. And we can be sure New Yorkers are happy to now have their biotech companies – like some of their sports teams – one happy New York-New Jersey family.

SCIENCE IS THE SNAKE OF SERENDIPITY

Where some might see the mysterious movement of serendipity leading Regeneron from one therapeutic domain to the next, Stahl sees the logical and steadfast pursuit of science. This dedication is without regard for what is paramount in so many other companies: patient population numbers and potential financial returns. "Through our history," says Stahl, "we have been fearless about entering any new areas if we believe we have some scientific insight to help patients."

For example, although now famous for eye drug Eylea, Regeneron started with a deep research effort in angiogenesis in oncology to get there. Regeneron cloned a group of new factors with a primary importance in developing and stabilizing blood vessels. To pursue work with these angiopoietins, the company formed an angiogenesis team to study the full processes by which new vessels are formed, how they become pathologic, and the potential to regress them if it was shown they were not wanted in certain areas.

Regeneron had reached the conclusion that macular and endothelial growth factors were probably primary to some diseases, but other factors like these angiopoietins could play a role. With that insight, the company independently engineered the VEGF Trap — a decoy receptor-molecule combining two distinct receptor components and a portion of an antibody molecule called the "Fc" or "constant" region – which became Eylea. "These two pursuits, angiogenesis and this engineering technology, came together for our entering this area of eye disease," says Stahl.

"This is a vignette of how we entered one area. But the same applies across all of these other therapeutic areas. We're in a wide diversity of biology areas, but each stems from initial biological insights and the pursuit of the science."

A great deal of that biological insight stems from Regeneron's interest in human genetic findings. "Our cholesterol program arose out of the genetic finding that people with a mutation in one copy of the PCSK9 gene have lower LDL," says Stahl. "In a 15-year observation period, these people also had an 88 percent reduction in cardiovascular disease and appeared to have no ill effects from having a loss of function mutation which inactivated one copy of their PCSK9." From that key observation, Regeneron moved forward to develop animal models that produced the same results in mice and monkeys, by creating antibody reagents that mimic the blocking function of the PCSK9. With that proof-of-concept, they were then able to show a dramatically lower LDL level in humans. The resultant drug is Praluent (Alirocumab), an antibody targeting LDL-cholesterol (LDL-C or "bad" cholesterol) and which is now tantalizingly close to FDA and EMA approvals.

Stahl points out that in Tarrytown, Regeneron has one of the largest mouse-genome engineering capabilities in the world. Working with the NIH, Regeneron is in the midst of a "knockout mouse project," deleting one gene at a time in the mouse genome to help understand how that affects health and disease. Also, the Regeneron Genetics Center was recently opened "to work hand-in-hand with this mouse biology and try to understand if there are other mutations in the human population that tell us about biology and disease." Now with one of the largest sequencing operations in the U.S., Regeneron expects, by year's end, to have sequenced 100,000 exomes, which make up 1 percent of the human genome and are expressed as proteins.

"We'll correlate that with phenotypes to look at susceptibility to health issues such as cardiovascular disease, high blood pressure, and high LDL," explains Stahl, "and conversely look at general health and a lack of disease, suggesting a protection that we may make use of."

He concludes: "All of this sequencing is providing new insights that will help us enter more therapeutic areas — like we entered the cholesterol area — based on the pursuit of genetic research."

THE NEXT SURE THING(S)

Along with Praluent, Regeneron awaits an array of approvals in coming months and years. These include Sarilumab, the company's antibody targeting IL-6R for rheumatoid arthritis, currently in a global Phase 3 program. The company and its research partner Sanofi plan to present new data and submit a BLA (biologics license application) in the U.S. by the end of this year. Stahl believes Sarilumab will prove useful for other inflammatory and immune conditions as well.

Another compound working through the clinic is "the unprecedented drug Dupilumab, which has shown encouraging efficacy in mid-stage trials for three distinct allergic conditions," says Stahl. Dupilumab is an antibody that blocks signaling of IL-4 and IL-13 and is currently undergoing study in atopic dermatitis, asthma, nasal polyps in patients with chronic sinusitis, and eosinophilic esophagitis.

However, true to the Regeneron way, Stahl seems more excited — and confident — the further up the pipeline he looks. He says there are "another 15 antibodies in clinical trial, including some based on new platform technologies." He's referring to Regeneron's own approach to the renaissance in immuno-oncology, based on the increasing realization that tumor cells have mechanisms to suppress the immune system. "A variety of molecules that block that interaction and rev up the immune system have been discovered. We are very active in this area," says Stahl.

This is in addition to what Stahl calls "bi-specific antibodies," where instead of reliance on endogenous immune response against a tumor, an antibody bridges and creates an artificial immune response. "One arm actually binds the tumor, and the other binds the T-cell — the immune cell — and activates it by clustering a surface protein just as if the cell had been naturally activated by the tumor. It's a new platform to turn on the immune system and direct it toward the cells you want to kill. We have one bi-specific antibody in the clinic now and five more ready to enter once we are convinced the approach is effective.

"We are just at the beginning of everything we can do with the science and these new drug platforms we're building. What keeps us coming to work everyday is not what we've already done, it's the exciting stuff still in the hopper."

A LIFE SCIENCES START-UP LEARNS TO PIVOT & OVERCOME ADVERSITY

By C. Yarbrough

JONATHAN LIM, M.D.
President and CEO of
Halozyme Therapeutics

A LIFE SCIENCES START-UP LEARNS TO PIVOT & OVERCOME ADVERSITY

CATHY YARBROUGH Contributing Editor @sciencematter

Jonathan Lim, M.D., was only 31 years old when he was appointed Halozyme Therapeutics' first president and CEO in 2003. During the previous two years, he was a management consultant at McKinsey & Company, advising C-suite executives of both start-ups and Fortune 500 companies in the healthcare industry. But, prior to Halozyme, which is headquartered in San Diego, Lim had not worked at a biotech or pharmaceutical company.

"I was flattered but surprised when Audrey offered me the job," said Lim, referring to the venture capitalist Audrey Viterbi, Ph.D., then CEO of Linkagene, an investor in Halozyme. "I didn't find out until later that individuals who were more seasoned and qualified had already turned down the offer because they realized the company was nearly out of money." Those other CEO candidates understood the challenges of quickly raising cash to fund operations. Lim did not. "I was unencumbered by knowledge or experience!" he joked.

That lack of knowledge helps explain why Lim took a "leap of faith" when he left McKinsey to join a start-up with only three months of cash on its balance sheet. His primary motivation was the desire to build and lead successful companies, the result of his experiences in founding a student-led medical journal at McGill University in Montreal, where he received his M.D. degree in 1997. "I was as excited by the process of creating something from nothing as I was about the content of the journal," he recalled. He was "bitten by the entrepreneurship bug."

During his 2003 to 2010 tenure as president, CEO, and board director, Halozyme grew from five employees and a market value of $5 million to 140 employees and peak market capitalization of almost $1 billion. Under his leadership, Halozyme also became a publicly traded company, raised $300 million from financings and corporate partnerships with Roche and Baxter, achieved FDA approvals for two medical products, and launched clinical trials of six additional investigational agents.

How did he do it? Halozyme's evolution to a fully integrated biopharmaceutical enterprise during the company's first seven years can be attributed to Lim's simple practice of seeking advice from, as well as hiring, people "smarter or more experienced than myself, or ideally both," he said. "If you put the right people together, the team can achieve great things, irrespective of the underlying technology. This practice also has served me well in each of my roles post-Halozyme."

FROM START-UP TO ACQUISITION IN 18 MONTHS

Three weeks after exiting Halozyme in December 2010, Lim launched a healthcare investment company, City Hill Ventures, at which he founds, funds, and leads life sciences companies. Eclipse Therapeutics, the first company he cofounded, was a Biogen Idec spinoff focused on therapeutics targeting cancer stem cells. City Hill was Eclipse's lead investor, providing $500,000 of seed capital. Eighteen months after it opened its doors in March 2011, Eclipse was successfully acquired for $10 million up front and up to $65 million in cash earn-outs by Bionomics, a global publicly traded biopharmaceutical company headquartered in Australia. Lim, chairman and CEO of Eclipse prior to the acquisition, now serves on Bionomics' board of directors.

When they launched Eclipse, Lim and his cofounders did not plan to sell the company so quickly. The acquisition resulted from a strategic process Eclipse

WHAT WOULD JONATHAN LIM, M.D., SAY TO SOMEONE WHO ASPIRED TO BUILD AND LEAD A LIFE SCIENCES COMPANY?

PAY YOUR DUES EARLY IN YOUR CAREER

Obtain an M.D., Ph.D., J.D., or M.B.A. degree. "Studying for an advanced degree trains your mind and gives you credibility and the capabilities to handle different situations," he said.

After receiving his M.S. degree from Stanford University and M.D. degree from McGill, Lim trained in general surgery at the New York Hospital/Cornell Medical Center and Memorial Sloan Kettering Cancer Center. He subsequently completed two years of NIH-funded postdoctoral training at the Dana Farber Cancer Institute while studying for an M.P.H. degree in healthcare management at Harvard University. While at Harvard, he also took a business school course on entrepreneurship and founded a short-lived electronic medical records dot-com named MDscope, which was unsuccessful in raising money during the dot-com bust in late 2001. "One lesson I learned from this experience was that, to make something work, you have to work on it full-time on a 24/7 basis, not just nights and weekends on the side while pursuing a full-time job or classwork in school," he explained.

Early in his career, he also conducted both basic and clinical research at the Salk Institute for Biological Studies in La Jolla, CA, and the Massachusetts Eye and Ear Institute in Boston. "These multidisciplinary experiences have allowed me to appreciate the business, scientific, and medical considerations involved with building and growing a biotechnology company," he said.

Learning should never stop. "Have the humility to continue to learn," he said, "and to ask questions and listen to other people."

THERE'S NOTHING LIKE LEARNING ON THE JOB

Lim encourages individuals who want to be entrepreneurs to take the leap at a stage in your career when you can afford to do so, but don't wait too long. "Putting all of your efforts and energy into an entrepreneurial venture and having your livelihood depend on it are very clarifying experiences," said Lim. Leading Halozyme was his defining experience in learning about entrepreneurship.

DEVELOP STRONG INTERPERSONAL SKILLS

"Entrepreneurs must have the passion, commitment, and empathy to motivate people around a common vision and achieve ambitious goals collectively as a team," said Lim, who regards his training as a physician and his numerous interactions with patients and other healthcare providers as helping him to develop effective interpersonal skills.

BE ULTRASELECTIVE IN RECRUITING PEOPLE

"It is more important to have great people on your team than to have a great technology," he said. "Great people can figure out how to make a company successful in spite of challenges that may arise with the underlying technology. The inverse is not always true."

FOLLOW YOUR "TRUE NORTH"

At Ignyta, Lim gives every employee and board member the book "True North," by former Medtronic CEO Bill George, because it "articulates a holistic theme of authentic leadership, including being true to yourself and to others, in order to be a more effective leader," he said.

"If you want to build and lead a life sciences company, it is really important to first know yourself and know why you are doing what you are doing, so that you can effectively pursue your purpose with passion," he said. "For me, my strong Christian faith and passion for helping patients are foundational for how I lead and interact with others. For other people, they may have their own beliefs or values that drive them in what they do. It is important to have the self-awareness to figure out for yourself what drives you before you seek to lead others, so that you have an internal compass that helps guide you through both the good times and the bad. Entrepreneurship and leadership are both really tough, but they are each nearly impossible if you don't know yourself."

undertook in 2012 when it needed cash to fund its growing operations. "Taking nothing for granted, we pursued multiple options in parallel by dual-tracking our financing and M&A discussions with VCs and biopharmaceutical companies, respectively," he said. "We did not have a preference a priori for the VC versus acquisition path. In the end, we selected the option with the best prospects for creating value for our investors." The up-front payment alone earned a greater than 300 percent internal rate of return on the investment for City Hill, Eclipse's primary investor.

"City Hill is a small, focused fund that has made a limited number of investments, chiefly because I was deeply involved, taking a hands-on, operational, or advisory role with each portfolio company, as I did with Eclipse and am currently doing with Ignyta," said Lim. "However, the model has evolved: I'm now running Ignyta on a full-time basis and hope to do so for a very long time, as it's the most exciting company with which I've ever been associated."

A STRATEGIC PIVOT AFTER A NEGATIVE CLINICAL TRIAL

Ignyta was cofounded in 2011 by Lim and internationally renowned rheumatologist Gary S. Firestein, M.D., to create an early molecular diagnostic assay for rheumatoid arthritis (RA) based on the epigenetics research of Dr. Firestein's lab at UC San Diego. However, the assay failed to perform in a critical clinical study conducted in April 2013. The negative results were "so clarifying that we were forced to reconsider our business model," said Lim. In addition, growing uncertainties about reimbursement as well as regulatory and intellectual property matters were challenging the molecular diagnostics market.

Lim and his team deliberated on various alternatives for Ignyta, including closing the company and distributing funds back to the shareholders. Because of the negative data and macroenvironment issues, the option of continuing the status quo was immediately ruled out. They instead decided to reinvent the company by quickly executing what Lim described as a strategic pivot that transformed Ignyta into a precision medicine company to concurrently develop therapeutics (Rx) and companion diagnostics (Dx) for cancers with specific oncogenes that are known to drive the growth and spread of tumors.

Ignyta's transformation into an integrated Rx/Dx company could not have occurred so quickly if not for its merger with Actagene Oncology less than three

weeks after Ignyta's negative diagnostic assay results. Actagene, another San Diego start-up funded by City Hill, was cofounded by Lim and Patrick O'Connor, Ph.D., former global research therapeutic area head for oncology at Pfizer. Actagene, at which O'Connor was CEO, was trying to raise $5 million. Ignyta had $5 million in its reserves. The companies' respective boards agreed to merge the two companies in May 2013, just four months after Actagene's founding. The merged company retained the Ignyta name. Lim described the merger as a synergistic combination of the two companies' genomic and epigenomic databases and Rx and Dx discovery and development capabilities.

"One of the greatest challenges of entrepreneurship is knowing when to keep going, quit, or change direction as a company when times get tough. Most entrepreneurs either don't know how to quit or are not able to take a step back and objectively assess and address adversity, so most of us keep going. Seizing the right moment to change direction due to either macroenvironmental or company-specific challenges and being able to implement the change rapidly before you run out of cash are keys to successfully growing a company," Lim said. "We capture this idea with our 'Crucible' value at Ignyta, which states that we 'confront all facts and data — no matter how sobering, and use adversity to raise our game and emerge stronger,' as we did in early 2013 with our strategic pivot."

In 2013, Ignyta also became a publicly traded company and in-licensed two compounds, one clinical and the other preclinical, from Nerviano Medical Sciences, a former oncology drug discovery facility of Pharmacia and Pfizer in Italy. The clinical-stage compound, entrectinib, is Ignyta's lead program. Under evaluation in two Phase 1/2 clinical trials, entrectinib received the FDA's orphan drug designation for nonsmall-cell lung cancer, colorectal cancer, and neuroblastoma, as well as a rare pediatric disease designation for neuroblastoma. As early as the third quarter of 2015, entrectinib could be in a pivotal registration-enabling study.

LEVERAGING A DIFFERENTIATED PLATFORM

In late 2014, Ignyta encountered a new growth opportunity. Teva Pharmaceutical Industries had decided to shift its strategic focus from oncology R&D and was selling four of its experimental compounds. One of those compounds was RXDX-105, which had a unique profile that inhibits three cancer-driving gene alterations that are activated in nonsmall-cell lung cancer, colorectal cancer, and other solid tumors.

"We knew what kinds of complementary therapeutic opportunities we were looking for, so as soon as we became aware of the Teva oncology R&D pipeline coming up for sale, we mobilized a multidisciplinary, 20-person 'SWOT team' to complete our initial due diligence," Lim said.

The competition for these compounds came from several biopharmaceutical companies and VCs, many of which were larger and had deeper pockets than Ignyta.

Seventeen days after creating that specialized team, Ignyta presented its proposal to acquire the four Teva drug candidates. Nine weeks after that (March 2015), Ignyta and Teva signed and announced their agreement.

Lim believes Ignyta prevailed in this competition because it put together a creative deal structure. "When a deal makes sense for both parties, both strategically and operationally, then it can happen very quickly," he said. "We also sold Teva's leadership on our team, vision, and capabilities, which were already in place and could be leveraged effectively to develop these new assets." In the release announcing the deal, Michael Hayden, Ph.D., president of global R&D and CSO at Teva, commented, "Ignyta's capabilities and focus in oncology will give these assets the best chance of realizing their potential for patients and of maximizing their value for Teva."

Ignyta also raised $42 million in financing that closed concurrently with its acquisition of the Teva assets. RXDX-105 is now in an Ignyta-sponsored Phase 1/2 clinical trial.

> *"One of the greatest challenges of entrepreneurship is knowing when to keep going, quit, or change direction as a company when times get tough."*
>
> **JONATHAN LIM, M.D.**

ACHIEVING A $225 MILLION MARKET CAP

Today, Ignyta has over 70 employees and a pipeline of six clinical and preclinical oncology compounds, all potential targeted cancer drugs and novel chemotherapies. Ignyta's pipeline agents will keep Lim and his team busy while the company's in-house scientists develop other compounds.

Ignyta's pipeline targets the majority of the molecular alterations known to drive the growth and spread of multiple solid tumors. Before enrolling individuals into its Phase 2 clinical trials, Ignyta plans to use its in-house diagnostics lab to screen patient tumor specimens for the molecular alterations targeted by the company's product candidates. Ignyta also will use the lab to periodically monitor the tumors' responses in the clinical trials. An in-house diagnostics lab that is CLIA (Clinical Laboratory Improvement Amendments)-certified and compliant with QSR (quality system regulations) is one of Ignyta's distinguishing features, Lim said, and the company believes it provides a competitive advantage. "Most oncology biotech companies rely on an outside diagnostic company to develop companion diagnostic assays for their drug candidates," Lim commented.

Investors have responded positively to Ignyta's transformation into an Rx/Dx precision oncology biotech company. More than $180 million has been raised since the company's inception. As of May 1, Ignyta's market capitalization was over $225 million. Lim has a 20-year vision for Ignyta to become the leading precision medicine company in oncology. L

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R&D Veteran William Comer Of NeuroGenetic – Focusing Through The Risk

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The chairman of Bristol-Myers summoned the head of R&D into his office. "Bill, go down and check out the ruckus on the street," he said. "Something about our new AIDS drug." When Dr. William Comer exited the front door of the company's New York City headquarters, he saw a small group of men marching around on the sidewalk, holding signs, blowing trumpets, beating drums, and chanting loudly. The year was 1988, the company chairman was then Richard Gelb, and the group, ACT UP, was new to Comer. He offered his hand to a gaunt, exhausted-looking man who introduced himself as Larry Kramer, widely regarded as the organization's leader and founder. Kramer said the group was protesting because it believed the company was "sitting on" a compound that could save lives — the preclinical anti-HIV candidate didanosine (2',3'-dideoxyinosine, or ddI). Comer patiently explained the early status of ddI, and in the end, pledged to make its development "the fastest on record."

Not only that, but he subsequently convinced the activist to join a groundbreaking drug-development steering committee including NIH directors, giving ddI top priority in the company's pipeline. Bristol-Myers would ultimately fulfill Comer's promise by taking the drug from early clinical stage to FDA review in only 18 months.

At the FDA hearing, just before the agency's scientific advisory board planned to adjourn for a final vote on recommending approval of ddI, the chair called a tardy witness. A scraggly figure approached slowly from the back of the room and apologized for arriving late. "I just attended the funeral for my lover," the man said. Then, in a weak and broken voice, he pleaded for the agency to make ddI quickly available to AIDS patients: "We don't have 10 to 12 years to wait!"

It was a pivotal moment. Comer says the reviewers looked at each other and, by general acclamation, decided to vote then and there to approve the drug. The persuasive witness, who was also diagnosed with HIV infection, was Larry Kramer. "Because of that experience, I made two resolutions," says Comer. "One, to employ the same steering-committee model in the company to accelerate development of our top-priority drugs, and two, always include a patient advocate on the team."

BIRTH OF A SERIES

I first heard the preceding story from Comer at this year's Biocom Global Partnership conference in San Diego, only because he happened to sit down next to me after his presentation for the company he now heads, NeuroGenetic Pharmaceuticals, which is developing new, unique drugs for neurodegenerative diseases such as Alzheimer's. He had already caught my attention by saying to the audience, "Prevention is the only way to defeat Alzheimer's. You can't cure a dead brain."

NeuroGenetic's lead candidate, NGP 555, is a small molecule modulator of the gamma-secretase complex designed to interrupt the early pathway of amyloid formation in the brain. Specifically, the drug redirects production of amyloid proteins from the toxic form deposited in diseased brains ($A\beta 42$) to nontoxic forms ($A\beta 37$ and $A\beta 38$). Key to the therapeutic strategy is treating patients before amyloid plaque reaches critical levels by using cognitive impairment as an early marker of the disease. The same drug mechanism, employing gamma-secretase modulators (GSMs) to inhibit the enzyme γ-secretase in the amyloid pathway, could also apply to other amyloid-based diseases such as cerebral vascular dementia, inclusion body myositis, and Alzheimer's dementia associated with Down syndrome.

Comer had a lengthy, distinguished career at Mead Johnson and Bristol-Myers Squibb, but the story of his entry into the industry is itself a lesson about the value of spontaneous, unguarded thinking in life, in science, and in business. In 1957, he had just graduated from Carleton College with a degree in chemistry and planned to enter a graduate program at

the University of Chicago to pursue a general interest in organic chemistry. During the summer break, he returned home to visit his parents in Iowa City and one day decided to take a walk on the University of Iowa campus. On impulse, he stopped in at the chemistry department, asked to speak with any available faculty, and was ushered into the chairman's office for an informal conversation. Assuming Comer was there to join the Ph.D. program, the chairman, Ralph Shriner, touted his own project, sketching out his ideas on the office chalkboard, then sought to recruit the young man into it.

But Comer frankly found none of it interesting. Taken aback, the chairman asked, "So what does excite you?" While waiting in the outer office, Comer had read an article in the latest issue of *Science* about the then-recent discovery of the neurotransmitter, serotonin. "I said it was exciting a single molecule like that works in the brain, the stomach, and in different ways all over the body, and I thought, by making similar molecules with slight differences, it might be possible to find one that works in the brain or in the stomach only."

The field of medicinal chemistry did not yet exist, but the chemistry chairman immediately phoned neighbor John P. Long, the chairman of the pharmacology department. Remarkably, Long had been reading the same article at that moment and said he wanted to speak with Comer immediately.

"He drove all the way across town to Prof. Long's office, and the three of us sat there all afternoon talking about serotonin," Comer recalls. "Next morning, the chemistry chairman offered me a teaching assistantship, full ride, in his department, and the pharmacology chairman offered me a research fellowship, and together we designed a program where I could synthesize serotonin analogs in chemistry and test them in animal models in pharmacology. I was naturally thrilled to be offered a package that would pay for my entire postgrad education. I called Chicago the next day and said I would not be coming there."

For the next four years, Comer took courses on opposite sides of the Iowa campus, majoring in both chemistry and pharmacology, making a few serotonin analogs, comparing them in animal models, and following "an interesting thesis." After gaining his Ph.D. in 1961, he began interviewing for a job, first mainly with chemical companies and later with pharmas. His last meeting was with the nutritional company Mead Johnson in Evansville, IN. There, echoing his first day at the University of Iowa, one interviewer was head of chemistry, and the other was head of pharmacology.

Comer recounts the meeting: "Mead Johnson had been trying to enter the drug business for about three or four years, and they weren't quite sure how. I said, 'Not to be presumptuous, but if you would offer me a job, where would my lab be, who would be my boss, and what project would I work on?' But they said, 'Oh, no, you don't understand. We want you to come and tell us what targets we ought to be working on.'"

THREE STRIKES, YOU'RE IN

At Mead Johnson, Comer's beginning project focused on the beta-adrenergic system, and it led to a hard lesson in industry thinking at the time. "We had the first beta blocker ever discovered, and as we were starting clinical trials, the head of marketing came in and asked, 'What kind of patients need their betas blocked, anyway?' No one had a clear answer at that point, so he killed the project. We were no longer the first beta blocker, and when we launched it a couple of years later, indicated for hypertension, it was already too late because ICI Pharmaceuticals had stepped in with propranolol [Inderal] in the meantime. That was a disappointment."

Comer's next project concerned the beta agonists, ultimately used in bronchodilators. Again, the lead compound was first-in-type, initially lacking a defined patient population, but after it showed excellent results in clinical trials, it ran into a toxicology roadblock. "They found some tumors in the second year of a tox study and shut down the whole thing," he says. "Several years later, I repeated the tox study and showed the tumors were not related to the drug at all. But by then Glaxo and other U.K. companies already had similar drugs on the market as bronchodilators, and they ruled the market for 20 years, just as propranolol had."

Working with a biochemist friend, Duane Gallo, Comer started a third program aimed at stopping cholesterol formation. "We came up with the first so-called HMG-CoA reductase inhibitors, but just when they were ready for clinical trials, the head of marketing killed the project because we didn't have a clear plan on how to pursue it clinically or commercially." Reflecting the times, the marketing head offered no help with forming such a plan. "Marketing was totally retrospective in view, not prospective," Comer says. "It wasn't a problem with the people — that's just what marketing was then."

OVER TO THE OTHER SIDE

Comer had reached the end of his rope. He started looking for another job. But the president of the company then, Wayne Davidson, offered Comer a new position outside of the research center and with a new title, director of new business development. "You can decide what programs we should work on and license in anything you think is an exciting innovation," the president said.

During his six-month tenure in the

position, Comer licensed in two of Mead Johnson's biggest-selling products on record, trazodone and cefadroxil, and had them on the market within a year. "The point is this: I had to talk marketing talk, and I had to convince our business people of the scientific merit of going into new areas where all the marketing strategies were not laid out ahead of time." He outlines the risk-mitigating strategy as a sequence:

1. License in a first-of-type compound.
2. Get it on the market quickly.
3. Make a good business with the product and impress the marketing people.
4. Immediately employ research in finding a better version of the compound — or another molecule with a different mechanism — to attack the same problem. Comer comments: "Research was not intended to be innovative because marketing wouldn't understand it, but research could make a better product."

Comer brought those principles with him after they installed him as VP of research, responsible for pharmaceutical discovery. He worked in Evansville for 20 years, staying with Bristol-Myers when it acquired Mead Johnson in 1967. But a seismic shakeup struck in 1982, when Bristol-Myers restructured — combining Bristol Labs, then in Syracuse, NY, with the Mead Johnson group and building a new research center in Wallingford, CT. Comer relocated to New York City to help put the organization together. Under a new head of research, Giulio Vita, formerly responsible for Bristol-Myers' international group, the company reorganized R&D into therapeutic-area units with discovery through clinical development in each therapeutic area, then a groundbreaking concept in the industry. Comer was responsible for three therapeutic areas.

"I liked the new structure, where you have a group of chemists, a group of biologists, and a group of clinical people all focused in cardiovascular or neuro or cancer," Comer says. "Every day, the chemists, the biologists, and the clinical people meet together, and all talk about how they can get a product into the clinic, move it through the clinic, and win approval expeditiously." At the same time, Comer realized Bristol-Myers had one of the slowest records in the industry moving products from discovery through development to the marketplace. "So it became a goal: How can we do it faster? How can we do it smarter?"

It was Comer's job to recruit someone to head each therapeutic area group. At first, he assumed clinical trials experts would make the best candidates, but then he realized such a person would tend to focus primarily on designing trials for maximum speed to market. "An area head must look toward how to design drugs." Comer decided the best candidate would be a kind of chemist/pharmacologist hybrid.

He says about half of the chosen therapeutic area heads were chemists, but very biologically oriented, actually in a then-nascent field that would become known as medicinal chemistry. "We required the TA (therapeutic area) heads to drive projects all the way to the finish line — and to make compounds that had the right properties, metabolic pathways, and so forth. So the pharmacokinetic and pharmacodynamic issues were addressed, hopefully solved, at the very earliest stages of the project."

After a few years in New York, the company added licensing to Comer's charges, where he deployed the staff of all Ph.D. scientists in an international matrix, some assigned by therapeutic area, others by geographic area. The idea was to create overlapping "silos" to comb through the territories thoroughly hunting for top-value drug candidates. "It worked out pretty well," says Comer. "We became known as the company that did a fabulous job of bringing in a lot of new discoveries at a very early stage."

One of the first drugs the company licensed and developed on Comer's watch was ddI, entering the unknown area of HIV but still within the company's strong anti-infectives tradition. At first, Comer says, it may have looked as though focusing all resources to speed a single drug along could have derailed his R&D group, but the actual experience ultimately taught the group and company invaluable lessons in how to move new medicines swiftly through the development pathway. One of the last drugs the company licensed and developed on Comer's watch was the cancer drug Taxol (paclitaxel) — in keeping with Bristol-Myers' unique oncology franchise. The new knowledge stretched from the corporate to the personal levels, looping back to the moment of truth before the regulatory committee.

"When Larry Kramer made his one-sentence statement at the FDA hearing, it absolutely got ddI approved immediately, and it had all happened in a very, very fast time. That was the key story because it convinced me of the need to have a patient advocate, especially in a very touchy clinical area. It was a first-of-type product in a new market, with nothing else out there that treats the problem. Patient advocates are absolutely essential — and so is total focus by the company on such a top-priority candidate."

FOCUS IN PRACTICE

So what does it mean for a company to place a single drug in development above all other priorities? Comer describes it as a challenging but rewarding process wherein some players must take a secondary role in the interest of speeding the lead candidate to the market.

"Once a year, I met with the leading scientists and marketing people, largely

divided by therapeutic areas — along with preclinical, clinical, and other departments, such as manufacturing and toxicology, that operated independently of the therapeutic-area concept — to prioritize the sequence and budgeting for all the pipeline projects. Of course, everyone wanted their own project to be number one, to be expedited ahead of everything else by manpower and money."

When the "number-one" concept began to soak in, Comer says the TA heads and project managers feared losing control of their resources to the needs of the lead project. And for ddI, internal resistance was even stronger because the anti-infectives market had slowed. "So it was a painful discussion, a lot of screaming and shouting," he says, "and once we more or less reached a consensus, we had to completely reorganize our clinical operations to do all of the ddI studies concurrently, not sequentially as usual."

Comer mediated the practical trade-offs of resources to push the top drug. "Somebody had to be the Supreme Court and make sure anything you could do with people or money, faster, went to that one project. And there were some very painful moments. Of course, when we got a quick FDA approval — going from IND (investigational new drug) to NDA (new drug application) in 18 months compared to an average of seven to eight years — everybody celebrated, because they realized that working together to push one drug forward did not hurt their projects, but it sure benefited the company."

From that point on, Comer says the company was committed to the "top-priority" strategy, and it repeated its record-breaking performance with the next lead candidate, Taxol, in only 15 months from IND to NDA approval. Industry peers began to show great interest in the company's historic move to multidisciplinary drug development. As a result, Comer believes, communication among companies and across disciplines inside companies improved generally. Within a few years, many other companies organized their R&D along similar lines. This was the mid- to late-1980s, as a golden age of pharma blockbusters dawned. But it, too, was not to last.

TECHNOLOGY STEERS A NEW COURSE

Licensing in early-stage compounds only worked to Big Pharma's benefit as long as the compound inventors lacked the large companies' ability and resources to move drugs through clinical development. Comer sees new technology as responsible for unseating that disparity by empowering academic labs and small companies to take their inventions further. A "systems biology" approach replaced much of the traditional discovery science such as massive screening, allowing more targeted screening based on a mechanistic understanding of disease. Biotechnology even brought a whole new medium of "drug" treatment, genetically engineered proteins, utterly foreign to the pharma establishment.

"With the new tools, you could make more molecules faster," Comer says. "You could test them faster in preliminary assays and in much smaller quantities. As a result, you needed fewer chemists, fewer pharmacologists, but more molecular biologists and data managers. We could run more programs, but with fewer people."

Meanwhile, large-pharma company R&D budgets had grown into the multi-billion dollar range, mostly shuttled to clinical development while discovery science and other innovative areas suffered big cuts. Why maintain risky, innovative programs inside the corporation when you can acquire the cream of the crop from outside sources?

"Many small companies grew out of academic labs, and they would go right to a new target, make fewer compounds, screen them faster, and get there first.

"If it isn't risky, it isn't innovation!"

BILL COMER

More of the Big Pharmas looked to the small biotechs to make the discovery and validate it before a big company would license it in."

A RETREAT FROM RISK

As the pharma companies reached the cusp of the license-in strategy, they also began to lose the lead in innovation. The total cost of Big Pharma R&D continued to soar despite internal cutbacks, yet the number of breakthrough, big-market drugs steadily fell. New life sciences companies came on the scene to capture markets and imaginations — sometimes reaching full integration at a smaller scale, remaining as prominent divisions inside their new owners, or becoming large companies on their own. Organizational dysfunction usually gets the blame for poor R&D productivity in Big Pharma, but a more likely culprit may be organizational chaos following the sudden, sweeping mergers of the times.

Comer was Bristol-Myers' top scientist when it merged with Squibb in 1989. By the earliest terms set by the companies' chairmen, the die was already cast: The remaining part of Bristol-Myers, the majority owner at 60 percent, would take charge of the business, including legal and administration, as well as sales and marketing, worldwide. As the 40-percent owner, Squibb would be in charge of the science.

Squibb imposed its own R&D structure and headed it with an academic profes-

sor who had no experience in the drug discovery and development area. Comer was moved to a new role as senior vice president of strategic management, where he put together some of the companies' best scientists and marketing experts to explore innovation opportunities in key therapeutic areas.

"It turned into a complete mismatch," he says. "The two company cultures were very different, and their organizational skill levels were very different. I had to move from working in Connecticut and in New York City, down to Princeton, where I must have appeared to be the invading enemy." Isolated from scientific and strategic business discussions, Comer finally called chairman Gelb to say he was taking an early retirement at age 55. After some 30 years, he was no longer working for Bristol-Myers.

DOWNSCALING TO INNOVATION

About a year previously, Comer's mother had died of Alzheimer's disease, thus piquing his old interests in disease mechanisms and neuroscience. He vowed to himself, "I don't know how, but I'm going to find out what causes this disease and try to help fix what's broken." He hoped to apply his record of success in multiple therapeutic areas to finding new approaches and bringing them to the market. But he found little encouragement in the halls of pharma.

"Nobody within the industry was doing anything about Alzheimer's. I saw some academic programs that seemed to be nipping away at the beginnings of it — especially at UC Irvine, UCSD, and The Salk Institute, all located around La Jolla, CA. I visited California to look around and found a postdoc at UC Irvine, Steve Wagner, working in a program at the heart of the amyloid approach. So he and I started a new company, and we merged it with a Salk development lab in La Jolla to become SIBIA Neurosciences. The people from Salk asked me to be CEO, but I just wanted to do drug discovery in the neuro area, where Salk owned many patents, rather than pursue diverse projects they had under way — and they agreed to that."

With about 100 people and less than $1 million in cash, the IP all held by Salk, Comer quickly scaled SIBIA down to a workforce of 18, all focused on the neuro candidates. "We built upon our expertise in receptor subtypes and high throughput screening with two corporate collaborations — Lilly and Novartis, and one with Bristol-Myers and Steve Wagner's group on Alzheimer's," he says.

By 1996, SIBIA had scored an IPO and placed five projects into clinical trials. But just as the company began to build a clinical development capability, it received an unsolicited acquisition offer from Merck & Co. in 1999. In need of funds, Salk pushed for the sale. "We were publically traded, but we sold the company for only $100 million, and $22 million went home to Salk, total profit, tax free," recalls Comer.

Mirroring his earliest days in the industry, Comer was learning how nothing in the life sciences start-up world moves in a straight line. After the experience with Merck and SIBIA, he would lead another company called Neurogenetics, that explored several patented approaches to Alzheimer's disease from Rudy Tanzi of Harvard along with Steve Wagner. By 2002-2004, a novel and selective approach to prevent Abeta42 and amyloid plaque formation had been discovered. The company became publicly traded as TorreyPines Therapeutics and developed a clinical agent for migraine and chronic pain.

In 2008, the board decided to sell the company with its pain project, but auction the Alzheimer's project separately. Comer placed the winning bid and restarted the Alzheimer's project as NeuroGenetic Pharmaceuticals in June 2009 with Tanzi and Wagner as cofounders. Maria Kounnas, the Alzheimer's project leader at TorreyPines, joined with Comer to further develop the project in preclinical development, pharmacokinetics, and toxicology and select NGP 555 as a preferred clinical agent, which is now in clinical trials.

"We then developed a stable formulation with once-a-day oral dosing; it gets to the brain and has a very specific mechanism for preventing Abeta42 formation. Although our company moves slowly with virtual staff and little money, it has been the culmination of drug development lessons — design experiments to get the most information from the fewest subjects, time, and money; understand any failures and then move on; assume success but expect the worst," says Comer.

As he once felt about the molecule called serotonin, he now feels about the new gamma-secretase modulators his company is pushing through development and hopefully to patients. "You can't treat Alzheimer's or other neurodegenerative diseases in the later stages, when the neurons have all essentially died," he maintains. "Investors and FDA regulators have also realized you have to prevent the damage, and thus you have to prevent the advanced stages of the disease. But prevention requires early diagnostics. Now, we can measure reduction of disease-related cognitive impairment as early as 26 weeks and measure early stages of amyloid deposits with PET scans."

So he's at it again — first-in-type treatment, expedited development, newer drugs in class coming along behind — and practicing a risk-accepting strategy he summarizes as, "If it isn't risky, it isn't innovation!" Dr. William Comer is a natural explorer who has found and traversed many new trails in his career, and he is trailblazing on for the industry even today. L

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The Evolution Of CRO Reimbursement: Shifting From Task-Driven Units To Desired Outputs

SUZANNE ELVIDGE Contributing Editor @suzannewriter

Over the years, pharma and biotech companies have looked to create better models to speed drug development and make it quicker, more efficient, and more effective, and this includes using the specialist expertise in clinical research organizations to carry out clinical development.

Building relationships with outsourcing suppliers is based around crafting the best possible agreement between the two partners. The most common form of late has been the task-driven model, which pays the vendor by the units and milestones achieved. However, the popularity of this has decreased, and moving away from task-driven agreements toward a more flexible model based on desired outcomes has been seen as the next step in the evolution of the biopharma-outsourcing partner relationship. This has potential to help all parties involved to keep aligned with the ultimate goal — that of safe clinical trials and high-quality data in a timely and cost-effective manner.

THE FIXED-PRICE CONTRACT

The fixed-price contract was the staple agreement for relationships between biopharma companies and their outsourcing partners/vendors in the 1980s and 1990s. These provided the vendor with the reassurance of a predictable income, which is especially important for smaller companies, and provided a powerful financial incentive to complete clinical trials efficiently and within (or before) the agreed timelines.

While the fixed-price model is still prevalent, sponsors continue to look for ways to incentivize performance beyond the traditional fixed-price structure, according to David Agrella, executive director, functional service partnerships at PPD, a CRO. "If a trial ran longer than planned or required more vendor effort to complete, the vendor lost money, and the fixed-price contracts left both sides without the ability to change aspects and renegotiate unless the study design fundamentally changed," explains Agrella.

THE BACKGROUND TO UNIT-BASED PRICING

The biopharma industry's growing dissatisfaction with the fixed-price contract drove a move toward unit-based or task-based contracts in the 2000s, where CROs are paid based on tasks achieved. Unit-based pricing uses straightforward measures based on the completion of tasks and a measure of the number of hours needed to perform each task, combined with the rates for the personnel performing the various functions of the trial (rates vary depending on a person's seniority).

Tasks in a clinical trial could include:

- sending out essential documentation and contract templates to potential sites
- generating a potential site list
- completing site selection
- completing site initiation visits
- completing recruitment by steps or in full
- carrying out monitoring visits
- writing monitoring trip reports
- processing data queries.

However, according to Agrella, payment for individual tasks, such as selecting sites, is difficult to administer by both the sponsor company and the CRO. It requires a level of tracking and reconciliation at the task level that may be onerous to both companies, when the efforts are better spent working toward achieving an output, such as an active site ready to enroll or an active site that has been screened. RFP specifications often will stipulate the number of sites to be activated. However, in practical terms, as much as 10 to 20 percent of sites may never become active for subject recruitment, and another 10 to 20 percent of activated sites may not recruit patients. If site activation and enrollment are the goal, then smaller tasks/units (i.e., site identification, site selection, site document collection, and site initiation) can be grouped into a larger output (i.e., site active and ready to enroll).

"In contrast with the fixed-price contracts of the 1990s, there is less direct financial incentive to complete a study ahead of schedule or find more efficient ways to deliver quality data under the terms of the unit-based project agreements unless supported through a governance structure or contracting terms. While the unit-based model remains the main method of contracting used today, it has not evolved in any great degree over the last 15 years," says Agrella.

Deirdre BeVard agrees that the unit-based model is still the default for most CROs, but that there are flaws. BeVard is the VP of development operations at Nektar Therapeutics, a clinical-stage biopharmaceutical company developing a pipeline of drug candidates that utilize its PEGylation and polymer conjugate

technology platforms. "With unit-based payments, we pay to recognize that someone has made the visit, for example, but there could be a lot of variability in the quality of the visit, dependent on the skills and the efficiency of the individual. However, the payment would be the same," says BeVard.

THE EVOLUTION OF THE DESIRED-OUTPUTS MODEL

To balance the incentives to complete a trial quickly and effectively with the desire to keep costs down, the biopharma industry has made a shift to a payment model that focuses on achieving the outputs to the quality standards required rather than just paying for tasks completed. This model has been growing in popularity since the mid-2000s, and is proving attractive to sponsor companies.

"The driver behind this move is that, for us, we have found that paying for time and materials is not the way to get the most value out of the relationship," says an outsourcing/partnership manager at a Big Pharma company.

As well as making a difference to the costs, because the desired-outputs model is outcome-driven, it should result in higher-quality data and, therefore, greater value for the sponsor. And while it may appear that these types of agreements are skewed in favor of the sponsors, there are advantages to the CROs. For example, more efficiently run trials and higher-quality outputs are likely to lead to shorter timelines and better margins and promote long-term relationships between sponsors and CROs. Through its focus on productivity, this model also will drive innovation.

"Ultimately, sponsor companies don't need lists and templates and selection visits; the industry needs active sites screening and caring for trial participants. And, if vendors are not paid until a site is active, then it is in their best interest to get as many good sites active, as quickly as possible, at a minimum of effort," says Agrella.

PUTTING THE AGREEMENT IN PLACE

According to the Big Pharma outsourcing/partnership manager, the most important step to creating a successful agreement is to have a good initial feasibility study. "We have found that the better the feasibility study, the better the contract and the relationship. Problems occur when the feasibility study is carried out before the protocol is finalized or the outcomes aren't agreed upon by the two parties."

One of the key points for the agreement is to define who is in control of the clinical trial process. Establish who has responsibility and authority. This includes decisions on choices of sites, project teams, and investigators.

"We believe the CRO has to be in charge of choices such as sites and investigators, rather than sharing the responsibilities. We have found that this avoids any hold-ups because the CRO is waiting on decisions from us as sponsor, and it reduces frustration. However, it does mean that the CRO must be accountable," says the Big Pharma outsourcing/partnership manager.

The options for operational control included in the agreement will vary depending on the chosen suppliers and their in-house experience and systems. As BeVard explains, "Operational control in the hands of the CRO can be more efficient if it means the CRO can follow its own systems and has the freedom to operate. However, some CROs have too many systems in place, which we feel makes the process too complicated. While we hand over day-to-day decision making — for example, choices of sites and investigators — we retain project-director-level control," she says.

In some cases, sponsors may want to include sites with lower rates of enrollment, for example, where they want to include a specific population or involve influential key opinion leaders. This option should be discussed as part of the feasibility process and included in the agreement, and recruitment should be monitored separately in order not to affect the CRO's outcome measures.

The agreement needs to outline deliverable-based milestones and set the quality standards. Because payments will be driven by both the completion of the deliverable and its quality, it is important to include protocols for monitoring the time, cost, and quality, all of which need to be assessed throughout the process by both the sponsor and the CRO. These agreements also need to be flexibile, taking into account that CROs may have to spend more time (and therefore, more money) on slower-recruiting sites.

The payment schedules can be critical, especially for some of the smaller CROs, and these terms can be discussed up front to suit both partners — for example, payment on percentages of sites enlisted or patients enrolled, rather than waiting for full enrollment. The payments also can be weighted to cover up-front costs — for example, money that has to be paid out to set up studies. "We don't tend to make a lot of up-front payments, but we can negotiate early milestones," says the Big Pharma outsourcing/partnership manager.

THE CHALLENGE OF REWORK

One of the challenges of the desired-outputs model is dealing with the issue of rework — for example, when a report is not up to the expected standards of quality or where poor choices of sites or key opinion leaders have been made. While the obvious response may simply be not to pay out, the situation may be a lot more complex than that.

The first step is to understand exactly what is behind the situation and who is culpable. It could be as a result of demands from the sponsor, such as too restrictive inclusion and exclusion criteria, or limiting the CRO to specific sites or key opinion leaders, or pressure on recruitment from competing studies. According to Charles Romano, senior director of Clinical Research at Amniox Medical, a subsidiary of TissueTech, incomplete or substandard projects may come down to incompetence or misconduct. However, this is rare, and the problems are more likely to be poor training or poor oversight

If the issue is entirely the fault of the vendor, then the rework should be done promptly and without charge. "We would only expect to pay if we bore some of the responsibility for the issue, and this is why clear accountability is important," says the Big Pharma outsourcing/partnership manager.

"While the unit-based model remains the main method of contracting used today, it has not evolved in any great degree over the last 15 years."

DAVID AGRELLA
Exec. Dir. of Functional Service Partnerships at PPD

However, sometimes partners need to make compromises, particularly to speed the remediation. In these cases, sharing the cost of the rework may be necessary. A lot of rework issues can be prevented by ensuring that the agreement has a degree of flexibility that allows partners to work closely together right from the beginning of the project.

CRO REIMBURSEMENT IN THE FUTURE

It is vital that CROs and sponsors bring innovation and value to the clinical trial process, as drug R&D is currently too slow and too costly. This will require better management of relationships, improved communication, and agreements that foster the concepts of partnership and collaboration. Both parties need to have a greater mutual investment in time, effort, and money.

"If both sides are prepared to both win and lose, this makes it more of a partnership," concludes BeVard. "However, there is still likely to be a space for transactional-type partnerships, as one size of agreement will never fit all projects and partners."

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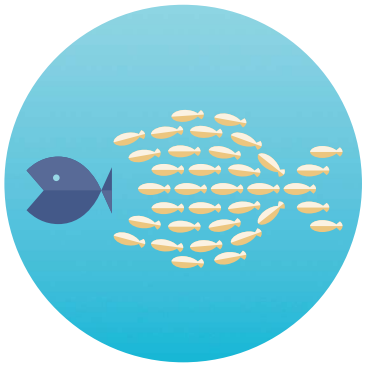
Eat Or Be Eaten: Controlling Your Fate In The Specialty Pharma M&A Feeding Frenzy

JAY MOHR



You can't blame specialty pharma companies for looking over their shoulders lately. For the smaller fish in the specialty pharma pond, a shadow circling overhead may turn out to be a Big Pharma at the top of the food chain seeking a rich source of R&D innovations or a growing revenue stream to supplement its business.

While a small company seeking an exit may welcome this prospect, a midsize specialty pharma might be less sanguine, hoping to escape becoming a predator's meal by bulking up with a few acquisitions of its own. As the M&A feeding frenzy intensifies at all levels, it's more important than ever for specialty pharmas to understand the dynamics of the waters they're swimming in. By staying alert to their own prospects as well as the appetites of those around them, these companies can achieve the best outcomes for their organization and its investors — whether as predator or prey.

The increase in specialty pharma M&A is easy to understand. With growth hard to come by in legacy business lines, higher-priced drugs used to treat conditions like cancer, rheumatoid arthritis, multiple sclerosis, and orphan diseases offer new possibilities. While some larger companies venture into their own specialty pharma directions (e.g., Bristol-Myers Squibb (NYSE: BMY) moving into oncology), it's more common for them to look for other companies that already have the important development work well under way — thereby minimizing the risk of clinical failure.

Among specialty pharma companies, we find two general types, each with its own concerns and priorities. On one hand, there are midsize companies such as Mallinckrodt Pharmaceuticals that are small enough to be acquired by a Big Pharma, but large enough to make acquisitions of their own. For these midsize specialty pharmas, active M&A is essential for maintaining their independence. On the other hand, we find smaller specialty pharmas. While being the smallest type of fish in the pond might seem like a precarious position, the reality is that the current seller's market can allow a tremendous range of options for the most appealing targets. These can range from an acquisition by either a midsize or large pharma — indeed, many small biotechs are built to sell from day one — to additional investment, strategic deals, partnerships, and even the opportunity to grow into big fish all on their own.

A SMART DIET FOR MIDSIZE SPECIALTY PHARMAS

The eat-or-be-eaten situation facing midsize specialty pharmas has led them to be particularly active in M&A. According to the HBM Pharma/Biotech M&A Report for 2014, of the $219.4 billion in worldwide biopharma M&A activity last year, midsize pharma companies such as Actavis and Shire accounted for nearly 60 percent of deal value — twice the level of large acquirers. These deals tend to follow an 80-20 rule; a handful of big acquisitions generate the most headlines, but the great majority of deal volume comes from small and midsize companies joining with even smaller ones.

The challenge facing midsize specialty pharma companies is that they want the same thing everyone else does: a postproof-of-concept asset or revenue-generating company with a product either close to commercial approval or already approved. But there aren't enough of these companies to go around, and those that are available will be costly. Rather than competing head-to-head for the most obvious targets, midsize companies should identify assets that either offer unique strategic value to their own businesses to justify a higher price or fly under the radar of other acquirers, easing competition. Often, smaller biotechs are more focused on science than business development and don't have the resources, expertise, or relationships to promote themselves effectively to poten-

"Agile and focused biotechs are a key source of innovation and expertise to revitalize the pharmaceutical industry."

tial partners or acquirers. Even the larger specialty pharma companies are bandwidth-constrained, limiting their ability to identify and/or pursue compelling acquisition opportunities.

While some midsize companies are inclined to wait for deals to come to them, this approach presents two problems. First, any target that makes its approach is doubtless shopping itself elsewhere as well, and this competition will drive its price higher. Second, this passive approach ignores the urgency to grow; while waiting for a suitable target to swim by, the company is all too likely to end up in the jaws of Big Pharma.

Horizon Pharma (NASDAQ: HZNP), a Chicago-based specialty pharma company with a diverse portfolio, illustrates a successful strategy by a midsize pharma to find the right deal for its situation. Horizon acquired Vidara Therapeutics in September 2014 for $660 million, an especially high multiple of 10X net revenue in an industry where 5X to 6X is more typical. While Vidara's products lie outside Horizon's historical areas of focus, Vidara's Actimmune, a treatment for the infections associated with chronic granulomatous disease (CGD), had been designated an orphan drug by the FDA. In addition to entitling its maker to FDA incentives and support, Actimmune's orphan status reflects the rare disease it targets and the lack of competition in its space, allowing breathing room for Horizon to overcome uneven performance and solidify its specialty pharma business. Perhaps equally significant, Dublin-based Vidara offered the opportunity for Horizon to structure the transaction to leave the surviving corporation with an Irish domicile and its much lower corporate tax rates. While the incidence of so-called tax inversions has slowed significantly following rule changes by the U.S. Treasury Department, it is a prime example of how the strategic case for an acquisition includes more than an analysis of a particular drug candidate.

MULTITRACK STRATEGIES FOR THE SELL SIDE

In today's seller's market, specialty pharma companies and their investors have the luxury of pursuing multitrack strategies that keep all their options on the table. Just three years ago, their opportunities might have been limited to either VC or private equity investment or a strategic deal. Today, they also can consider mezzanine funding, follow-on rounds from current venture investors, IPOs, partnerships with global pharma companies, or even regional deals in other parts of the world that allow them to retain R&D and commercialization rights in the U.S. Far from being seen as desperate or indecisive, this approach — now being pursued by some companies beginning at the earliest stages of development — is seen as a position of strength by a smart company that knows how to maximize its value.

For a multitrack strategy to be effective, a potential acquisition must be at least as viable and appealing as any other option. As on the buy side, sell-side suitors must be both active and informed. This begins with the definition of a strong business case even for development-stage assets: What is the size of the opportunity, and how is it supported through rigorous primary research and discussions with industry opinion leaders, in-the-trenches prescribers, and payers? In our own multi-track engagements, we typically start with a comprehensive commercial assessment to ensure the company's business case is fully developed before beginning any real partner outreach. Since the size of any deal is directly related to the nature of the opportunity, it is to the smaller company's benefit for the discussion to focus on the size of the pie, not just how it will be divided. This is most easily achieved through a robust commercial assessment.

In addition, when a smaller company is pitching a partnership or acquisition to a larger one, it is critical to demonstrate a credible understanding of the potential partner's market, the gaps in its R&D pipeline, and the mutual benefits of an acquisition and how each is supported by the smaller company's business case. By the smaller company taking on the task of doing much of the groundwork for potential partners, acquirers, or investors, it allows these parties to focus on validating a proposed strategy rather than creating one from scratch — a much less time-consuming endeavor which both eases deal-making and potentially increases the size of the transaction.

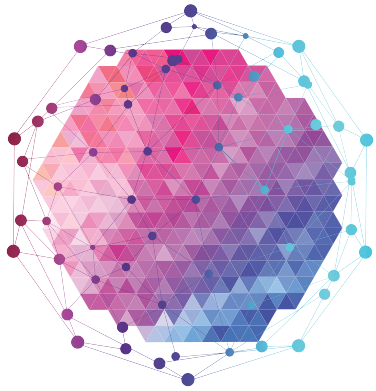
As an example, Civitas Therapeutics pursued a successful multitrack strategy in 2014. Spun out of Alkermes (NASDAQ: ALKS), an early developer of drug delivery platforms, Civitas focused on developing an NTE (new therapeutic entity) for advanced Parkinson's disease. While preparing for an IPO seeking to raise $80 million, the company was instead acquired by Acorda Therapeutics (NASDAQ: ACOR) hours before it was scheduled to go public for $525 million in cash.

Whatever path — or paths — specialty pharma companies choose, from a built-to-sell strategy to long-term independence backed by patient investors and willing partners, the current outlook is promising. With most common diseases adequately served by available treatments, agile and focused biotechs are a key source of innovation and expertise to revitalize the pharmaceutical industry as a whole. This gives them unique value to investors, partners, and acquirers alike — and allows greater freedom to control their own destinies. So long as the appropriate value-maximizing strategies are used, for once the supposed prey is getting to dictate if, when, and how it is to be eaten.

Jay Mohr is the managing director and founding member of Locust Walk Partners (www.locustwalkpartners.com), a firm focused on building biopharma companies through transformative transactions. He has more than 20 years of experience in the biopharmaceutical industry.

Biosimilar mAbs: Expanding The Global Biosimilar Market

CLIFF MINTZ Contributing Editor



After almost a decade of debate, there is now a generally agreed upon definition for biosimilar molecules: a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference product) that demonstrates similarity to the reference product in terms of quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise.

Since 2006, 16 biosimilar products have received marketing authorization in Europe (Table 1). Of these so-called "first-generation biosimilars," eight were different biosimilar versions of filgrastim (G-CSF), and five were biosimilar copies of different erythropoietin (EPO) molecules. Typically, these products are sold at prices ranging from 25 to 40 percent less that the corresponding branded molecules.

Yet, despite discounted prices, uptake of biosimilars has been slower than anticipated, and successfully commercializing them has been challenging. One of the reasons for this, according to Roman Ivanov, VP of R&D for Biocad, a Russia-based biosimilar development company, is that "years ago the medical community was not ready for nonoriginator products. Many doctors were overwhelmed by the complexity of biologics, did not really understand what biosimilars were, and were reluctant to prescribe them." Further, Magdalena Leszczyniecka, president and CEO of Cambridge, MA-based STC Biologics, a biotechnology company that specializes in biosimilar analytics and process development, suggested that regulatory confusion (mainly in the U.S.), coupled with quality and safety questions promulgated by innovator companies, has historically hindered first-generation biosimilar acceptance and uptake.

However, first-generation biosimilars like G-CSF and EPO have continued to garner increasing market share since 2010. Carol Lynch, global head of biopharmaceuticals & oncology injectables at Sandoz, pointed out that in 2013 its biosimilar G-CSF (Zarzio) outperformed its reference standard (Amgen's Neupogen), and it is currently the top prescribed daily G-CSF in Europe. Likewise, biosimilar EPO now accounts for ~60 percent of EPO prescriptions in Germany. Nevertheless, Kiran Mazumdar-Shaw, chairperson and managing director of Bangalore, India-based Biocon, believes that lessons learned from early commercialization experiences with first-generation products and much-improved product awareness will allow the next generation of biosimilars to more easily penetrate and quickly garner significant market share.

BIOSIMILAR MONOCLONAL ANTIBODIES: THE NEXT GENERATION

In 2013, global sales for eight branded monoclonal antibody (mAb) products that are used to treat a variety of chronic immunoinflammatory diseases and oncology indications was approximately $55 billion. Over the next five years, all of them will lose patent protection in Europe, and seven will no longer be patent-protected in the U.S.. Moreover, in May 2012, the European Medicines Agency (EMA) created a marketing authorization framework for mAbs and related products. These factors coupled with: 1) rising global biologics prices, 2) cost-saving strategies implemented by national healthcare agencies, hospitals, and third-party payers, and 3) clearly defined regulatory pathways for approval of biosimilars have induced a number of pharmaceutical and biotechnology companies to create biosimilar versions of several of the top-selling branded mAbs.

To date, biosimilar versions of Enbrel, Remicade, Rituxan, Humira, Herceptin, Avastin, and Lucentis are in early- to late-stage clinical testing in Europe and the U.S. The most advanced of these is SB4, a biosimilar version of Enbrel and Inflectra, a Remicade biosimilar. In 2014, the EMA agreed to review a market authorization application for SB4, and a biologics licens-

ing application (BLA) for Inflectra (infliximab) was filed with the FDA in 2014. Additionally, several biosimilar mAbs — Etanar (etanercept), Reditux (rituximab), Kikuzubam (rituximab), BCD-020 (rituximab), Exemptia (adalimumab), Herzuma (trastuzumab), and CanMab (trastuzumab) — are already being sold in various emerging markets.

Finally, in 2013, Inflectra and Remsima (infliximab) became the first biosimilar mAbs to receive marketing authorization in Europe. The EU marketing authorization for these products is considered a pivotal event in the commercialization of biosimilar mAbs because, prior to their approval, it was not clear whether or not biosimilar versions of mAbs could withstand the scrutiny of the comparability exercise given the molecular complexity of mAbs (as compared with simpler proteins like G-CSF and EPO). Also, both infliximab biosimilars have been approved in Canada, Korea, and Japan.

REMAINING ISSUES

There are several contentious issues that must be resolved before biosimilars can reach their full commercial potential. The first of these is indication extrapolation, a process by which a biosimilar is approved for all clinical indications held by a branded reference product with clinical data (generated during the comparability exercise) for only a subset of indications.

Biocon's Mazumdar-Shaw offered, "Indication extrapolation reduces the cost of clinical development and allows for larger discounts that directly benefit patients and healthcare providers." Sandoz's Lynch and STC Biologic's Leszczyniecka emphasized that indication extrapolation for biosimilars is essential for greater patient access and also ensures that biosimilars can compete with branded molecules. Biocad's Ivanov was even more sanguine about indication extrapolation. "It is absolutely critical for commercial success because it substantially reduces development costs." He added, "Without it, there is no sense in developing biosimilars at all." However, he cautioned that indication extrapolation may not be appropriate when originator molecules are approved for divergent therapeutic indications diseases where the mechanism of action may be different, e.g., autoimmune diseases vs. oncology.

Historically, the EMA has allowed indication extrapolation for all biosimilars that have received marketing authorization. This was the case for Inflectra and Remsima, which received market authorization in Europe for all six clinical indications associated with the originator product Remicade. In contrast, Health Canada approved Inflectra and Remsima for only four of six indications, citing minor structural differences with the reference product that might affect therapeutic efficacy for the remaining two indications. "Analytical comparability data suggested that the mechanisms of action [efficacy] may be different for the remaining two indications," said Leszczyniecka. Also, she cautioned, "It is likely that the FDA will impose the same level of scrutiny for biosimilar mAbs as Health Canada, given the FDA's emphasis on the analytical portion of the comparability exercise."

Another hotly debated topic is interchangeability/substitution, the ability of two products to be exchanged or substituted at the pharmacy level (without consulting the prescriber) without any risks or significant adverse effects on a patient's health. From a regulatory standpoint, interchangeability/substitution is a possibility in Europe, the U.S., and other markets. Not surprisingly, this practice is opposed by innovator companies and embraced by biosimilar manufacturers. While interchangeability/substitution has not been granted to previously approved biosimilars, Lynch, Ivanov, and Mazumdar-Shaw all believe that it will eventually become a reality in most markets. However, both Lynch and Mazumdar–Shaw were quick to point out that its importance will vary with individual products. "For retail-dispensed chronic-care products like those used to treat autoimmune diseases such as rheumatoid arthritis, interchangeability/substitution will be important. It will be less critical for oncology biosimilars which are usually dispensed in a hospital or clinical settings," said Lynch.

Finally, in recent years, the naming/classification system used for biosimilars has come under attack by innovator companies. At issue is whether biosimilars should be given the same International Nonproprietary Name (INN), or generic names, as innovator products. Brand-name drugmakers want biosimilars to have unique INNs to distinguish biosimilars from their products, citing patient safety and possible problems with adverse event reporting. Sandoz's Lynch emphatically offered, "The current system has worked well for biosimilars for over a decade, and there is no need to introduce any changes." Similarly, Biocon's Mazumdar-Shaw agreed with Lynch and warned, "Any changes to the current INN system for naming biosimilars will introduce unfair bias and unfair marketing advantages to innovator companies." Nevertheless, biosimilar naming and INN designation remains a hotly contested topic.

WHAT NEEDS TO BE DONE TO MOVE FORWARD

There are several issues that must be addressed to ensure the next generation of biosimilars is successfully commercialized. First, physician/healthcare provider education and engagement are of paramount importance. "Engaging the medical community via key opinion leaders will be vital to validate the science used to develop biosimilars and to ensure physicians that biosimilar quality, safety, and efficacy are similar to their branded counterparts," said Ivanov. Likewise, Sandoz's Lynch said, "We need to educate physicians to get them more comfortable with the concept of indication extrapolation, which will be essential to support a sustainable business model for biosimilar mAbs." Moreover, STC Biologics' Leszczyniecka emphasized that educating and engaging other stakeholders, especially payers, pharmacy benefits management companies, and specialty pharma firms, will be critical for appropriate formulary placement and successful commercialization of biosimilars.

Second, Mazumdar-Shaw indicated that "There is much misinformation being spread about biosimilar 'unknowns' that is hurting biosimilar credibility among prescribers." And this will likely

Table 1

NAME	ACTIVE SUBSTANCE	MANUFACTURER	APPROVAL DATE	CLINICAL INDICATION
Abseamed	epoetin alfa	Medice Arzneimittel Pütter GmbH & Co. KG	2007	Treatment of anemia associated with chronic renal failure (CRF) in adult and pediatric patients; treatment of anemia associated with cancer chemotherapy
Accofil	filgrastim	Accord Healthcare Ltd	2014	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Bemfola	follitropin alfa	Finox Biotech AG	2014	Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies: Stimulation of spermatogenesis in men
Binocrit	epoetin alfa	Sandoz GmbH	2007	Treatment of anemia associated with CRF in adult and pediatric patients; treatment of anemia in adult patients receiving chemotherapy
Biograstim	filgrastim	AbZ-Pharma GmbH	2008	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Epoetin Alfa Hexal	epoetin alfa	Hexal AG	2007	Treatment of anemia sssociated with CRF in adults; treatment of anemia associated with cancer chemotherapy
Filgrastim Hexal	filgrastim	Hexal AG	2009	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Grastofil	filgrastim	Apotex Europe BV	2013	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Nivestim	filgrastim	Hospira UK Ltd.	2010	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Omnitrope	somatropin	Sandoz GmbH	2006	*Infants, children and adolescents:* Growth disturbance due to insufficient secretion of growth hormone (GH); growth disturbance associated with Turner syndrome; growth disturbance associated with chronic renal insufficiency; Prader-Willi syndrome for improvement of growth and body composition *Adults:* Replacement therapy in adults with pronounced growth hormone deficiency
Ovaleap	follitropin alfa	Teva Pharma B.V.	2013	Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies: stimulation of spermatogenesis in men
Ratiograstim	filgrastim	Ratiopharm GmbH	2008	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Retacrit	epoetin zeta	Hospira UK Limited	2007	Treatment of anemia associated with CRF in adult and pediatric patients; treatment of anemia associated with cancer chemotherapy
Silapo	epoetin zeta	Stada Arzneimittel AG	2007	Treatment of anemia sssociated with CRF in adult and pediatric patients; treatment of anemia associated with cancer chemotherapy
Tevagrastim	filgrastim	Teva GmbH	2008	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases
Zarzio	filgrastim	Sandoz GmbH	2009	Treatment of neutropenia associated with cancer chemotherapy and infectious diseases

continue as brand companies seek to protect multibillion-dollar drug franchises. In support of this, Amgen successfully sued the Norwegian government to prevent government-mandated automatic substitution of Neupogen with biosimilar versions of G-CSF. However, Mazumdar-Shaw opined that "Health economics will ultimately take precedent over fearmongering, and over time biosimilar safety/efficacy data will speak for itself."

Finally, both Lynch and Leszczyniecka agreed that the commercialization strategy for the biosimilar mAbs will more closely resemble that for branded molecules as compared with the more traditional generic drug approach used for first-generation biosimilar commercial launches. Further, Lynch said, "From a commercialization perspective, one of the key things that Sandoz has learned over the last decade or so is that there is no one-size-fits-all solution for biosimilars." She added, "In terms of Sandoz's commercialization strategy, product launches will be tailored for specific market dynamics and based on prescribing habits/reimbursement strategies for individual molecules."

Despite rising biologics prices and skyrocketing healthcare costs for the past decade, the global biosimilar market is still in its infancy. And, while some missteps were made commercializing first-generation biosimilars, biosimilar manufacturers are still learning as the global market continues to evolve. Therefore, today's biosimilar mAbs are likely to fare much better both commercially and economically than their predecessors. L

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M.S. RAO, PH.D.

Today's successful CEOs understand that seeing "The Big Picture" can help avert organizational challenges *and* overcome them. Visionary CEOs like Richard Branson, Warren Buffett, and Lou Gerstner all have an innate ability to see the big picture — i.e., they could see what others could not.

THE IMPORTANCE OF CONCEPTUAL SKILLS

Social psychologist Robert Katz says that each of the three levels of management — low, middle, and top — has its own need for technical, human, and conceptual skills. For instance, at low-level management, more technical skills and fewer conceptual skills are needed. At the middle level, there is equal need for technical, conceptual, and human skills. And at the top level, there is more need for conceptual skills and less need for technical skills as the leaders become involved in strategic management. The need for human skills (i.e., the ability to work well with others), however, is evident at all levels of management. Hence, leaders and chief executives must possess conceptual skills to see what cannot be seen by others, to have the vision to make decisions according to the big picture.

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EMPHASIZE ETHICAL VALUES

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He shares his profits through philanthropic activities.

It is essential in the current competitive world to see the big picture to avert organizational challenges. Hence, leaders and CEOs must learn lessons from leaders such as Buffett to see the big picture to minimize organizational challenges and maximize organizational effectiveness.

Professor M.S. Rao, Ph.D., is an international leadership guru and the author of 30 books, including the award-winning *21 Success Sutras for Leaders*, which has been ranked as one of the top 10 Leadership Books of the Year - 2013 by San Diego University. His vision is to build one million students as global leaders by 2030.

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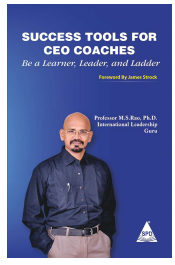

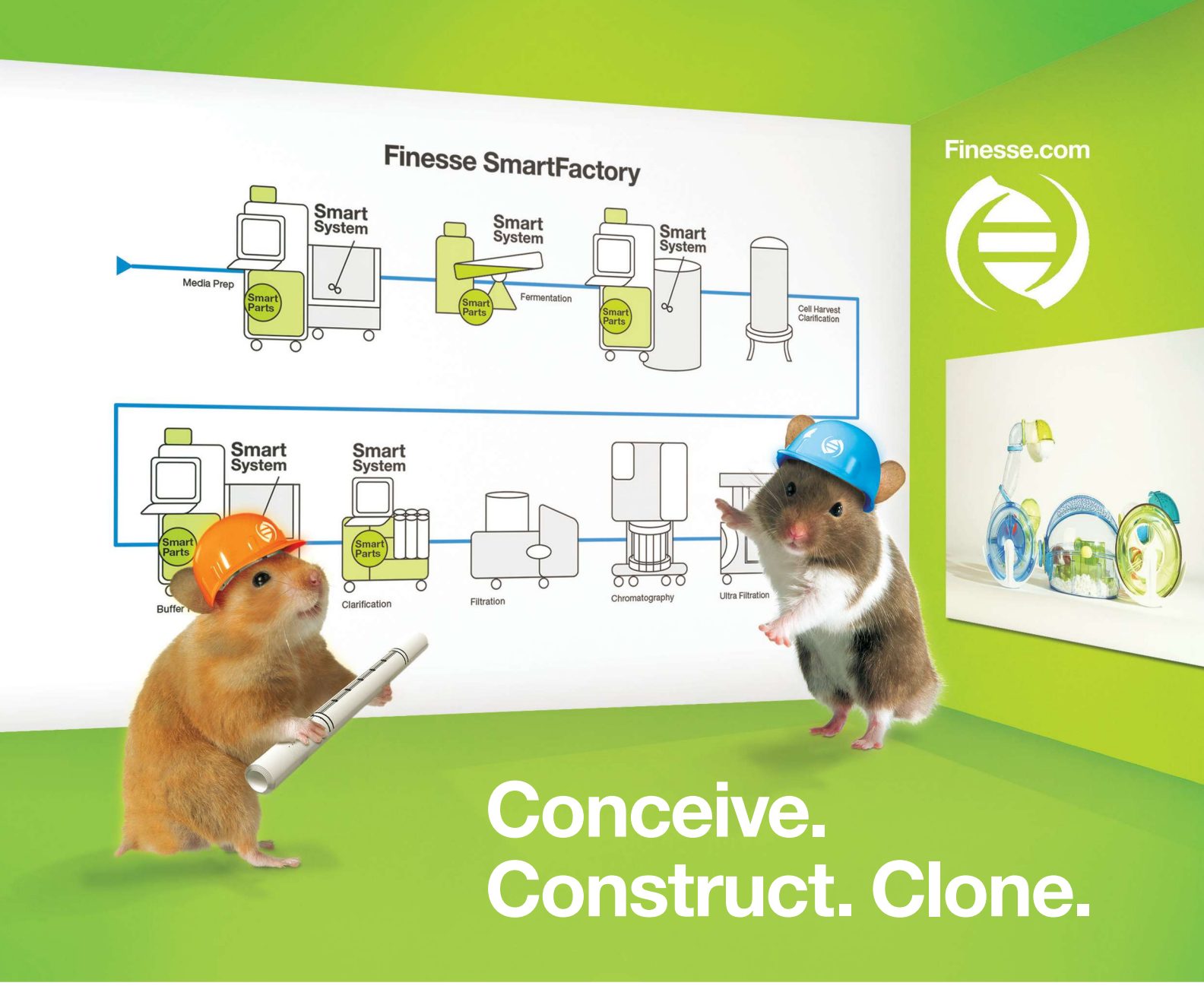

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