Life Science Leader

Connect. Collaborate. Contribute.

AUGUST 2017

SANAT CHATTOPADHYAY
President, Merck
Manufacturing Division

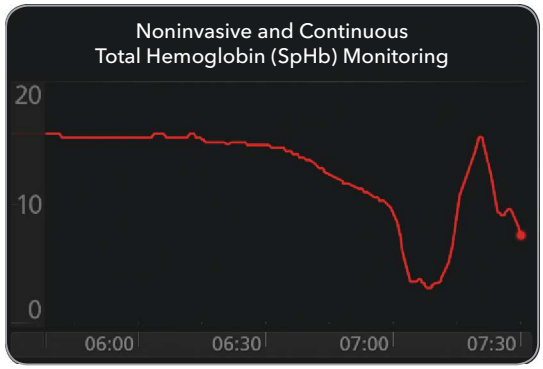
Shaping Merck's Manufacturing Future

p. 16

For transfusion decisions made in real-time, don't you need real-time data?

SpHb noninvasively provides continuous visibility to changes in hemoglobin, which may help clinicians make more informed and timely transfusion decisions.

Peer-reviewed studies have found that using noninvasive SpHb monitoring in conjunction with invasive blood samples has helped clinicians to:



Reduce Unnecessary Transfusions

in low blood-loss surgery:

- > 87% reduction in transfusion frequency (from 4.5% to 0.6%)[1]
- > 90% reduction in average units transfused (from 0.1 to 0.01 units per patient)[1]

in high blood-loss surgery:

- > Reduction in the percentage of patients receiving 3 or more units from 73% to 32%
- > 47% reduction in average units transfused (1.9 to 1.0)[2]

Initiate Timely Transfusion When Transfusions Are Needed

in high blood-loss surgery:

- > Transfused an average of 41 minutes sooner[2]

NOW Available in Philips Monitors

PHILIPS

For more information, visit

www.masimo.com

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician. See instructions for use for full prescribing information, including indications, contraindications, warnings, and precautions.

Clinical decisions regarding red blood cell transfusions should be based on the clinician's judgment considering among other factors: patient condition, continuous SpHb monitoring, and laboratory diagnostic tests using blood samples. SpHb monitoring is not intended to replace laboratory blood testing. Blood samples should be analyzed by laboratory instruments prior to clinical decision making.

[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9.

[2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4.

Study Protocol: In each group, if researchers noted SpHb trended downward below 10 g/dL, a red blood cell transfusion was started and continued until SpHb trended upward above 10 g/dL. The transfusion threshold of 10 g/dL was predetermined by the study protocol and may not be appropriate for all patients. Blood sampling was the same for the control and test group. Arterial blood was drawn from a 20 gauge radial artery cannula into 2 mL EDTA collection tubes, mixed and sent for analysis by a Coulter GEN-S Hematology Analyzer.

PLCO-001129/PLMM-10560A-0717
PLLT-10328A

In today's complex pharmaceutical laboratory environments, you need your researchers concentrating on one thing: their *science*. And that means your instrumentation and IT systems must work together to support the critical work your scientists do. Our highly qualified OneSource Information Services team is the *only* global life sciences organization where IT and scientific expertise work together to really understand the way your workflow *works*. Want to accelerate your scientific productivity through high-quality, reliable, compliant IT processes? That's what will happen when you engage OneSource.

www.perkinelmer.com/onesource

PerkinElmer®
For the Better

CONTENTS

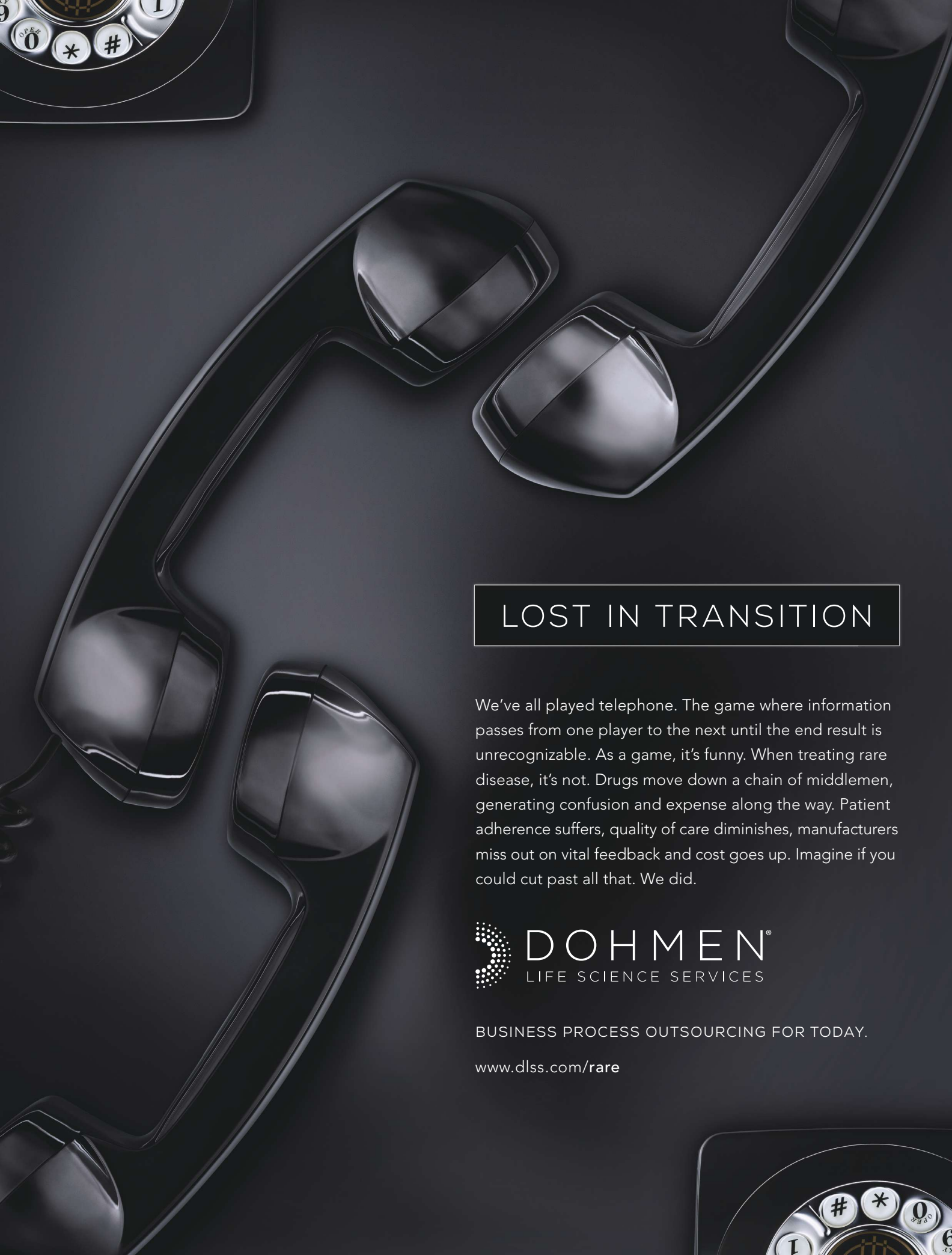
Welcome to

Life Science Leader

AUGUST 2017 VOL. 9 NO. 8

@LifeSciLeader1 linkedin.com/company/life-science-leader facebook.com/LifeScienceLeader WWW.LIFESCIENCELEADER.COM

LIFE SCIENCE LEADER (ISSN: 21610800) Vol. 9, No. 8 is published monthly by Jameson Publishing, Inc. at Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. Phone (814) 897-9000, Fax (814) 899-5587. Periodical postage paid at Erie, PA 16510 and additional mailing offices. **SUBSCRIPTION RATES** For U.S. based subscribers, $295 for one year. If your mailing address is outside the U.S. the subscription price is $445 for one year. **POSTMASTER:** Send address corrections (Form 3579) to Life Science Leader, Knowledge Park, 5340 Fryling Road, Suite 300, Erie, PA 16510-4672. **PUBLICATIONS AGREEMENT:** No. 40722524 c/o AIM, 7289 Torbram Road, Mississauga, ON L4T 1G8.



LOST IN TRANSITION

We've all played telephone. The game where information passes from one player to the next until the end result is unrecognizable. As a game, it's funny. When treating rare disease, it's not. Drugs move down a chain of middlemen, generating confusion and expense along the way. Patient adherence suffers, quality of care diminishes, manufacturers miss out on vital feedback and cost goes up. Imagine if you could cut past all that. We did.

DOHMEN®
LIFE SCIENCE SERVICES

BUSINESS PROCESS OUTSOURCING FOR TODAY.

www.dlss.com/**rare**

Has Your Company Ever **Been Held For Ransom?**

ROB WRIGHT Chief Editor

Imagine showing up at your office on a bright summer morning only to be greeted by the following note written on a whiteboard posted in the lobby, "All network services are down. DO NOT turn on your computers! Please remove all laptops from docking stations & keep turned off — no exceptions." You soon learn that your company is the victim of a cyberattack, and its network is being held hostage by ransomware, malicious software that blocks access to files and data until a ransom is paid. Not only will you not be able to finish the project you have been working on for the past day/week/month/year (not today anyway), but you may have to rebuild all of the painstakingly created documents for the project — from scratch. Have you ever experienced such a ransomware nightmare? The person interviewed for this month's cover feature has.

Sanat Chattopadhyay is the president of the Merck Manufacturing Division (MMD) and an EVP on the company's executive committee. During the writing of this article, on Tuesday, June 27, 2017, according to an article appearing in the *Washington Post*, his company was among dozens of businesses affected by a sprawling cyberattack. I was a bit unplugged from the daily news as I was deep in the process of finishing up the article and only became aware when another Merck executive called (regarding a completely different project) to inform me that we would need to reschedule our planned phone call as a result of the attack. I suddenly understood why my recent emails to Merck about the Chattopadhyay article had gone unanswered. So I picked up the phone and called Charlie McCurdy, director of global communications for MMD, to make sure we were still on track for completing this month's feature. And while I was relieved to be told "yes," I was even more pleased to learn, albeit briefly, how quickly the 60,000 member organization had rallied to address their current challenge. Because patients in need don't want to hear that their life-sustaining medicine can't be delivered just because you can't send an email. And while cyberattacks are serious, I am confident, given the company's 125-year history of delivering medications around the globe during stock market crashes, wars, natural disasters, and the like, that Merck will successfully overcome this as well. But will Merck and other companies pay the ransom? If so, what guarantee do they have that, once paid, the extortionists won't keep coming back for more? Is it worth it?

I have often pondered such questions when reading of Somalian pirates, who from 2005 through 2013, netted $400 million in ransom payments for 179 vessels hijacked off the coast of Somalia and the Horn of Africa. But this is chump change in comparison to the costs associated with ransomware. According to a May 2017 *Newsweek* article, not only is ransomware on the rise (i.e., mobile ransomware has risen by over 250 percent during the first few months of 2017), but Cybersecurity Ventures predicts the damage caused by various cyberattacks, beyond just the payment of ransoms, will exceed $5 billion in 2017 alone!

If your company has ever had a cyber/ransomware attack, email me and tell us about the headaches that were caused and the solutions you enacted to save your productivity. L

Life Science Leader

AUGUST 2017 VOL. 9 NO. 8

LIFE SCIENCE LEADER
5340 Fryling Rd., Suite 300
Erie, PA 16510-4672
Telephone: 814 897 7700
Fax: 814 899 5587

WWW.LIFESCIENCELEADER.COM

CEO
Jon Howland / Ext. 203
jon.howland@lifescienceconnect.com

EDITORIAL DIRECTOR
Dan Schell / Ext. 284
dan.schell@lifescienceleader.com

CHIEF EDITOR
Rob Wright / Ext. 140
rob.wright@lifescienceconnect.com

EXECUTIVE EDITOR
Wayne Koberstein
wayne.koberstein@lifescienceleader.com

EDITORS
Louis Garguilo
louis.garguilo@lifescienceconnect.com

Bob Marshall
bob.marshall@lifescienceconnect.com

Ed Miseta
ed.miseta@lifescienceconnect.com

Anna Rose Welch
anna.welch@lifescienceconnect.com

VP OF AUDIENCE DEVELOPMENT
Michael Bennett
michael.bennett@lifescienceconnect.com

STRATEGIC PARTNERSHIPS/BUSINESS DEV.
Mike Barbalaci / Ext. 218
mike.barbalaci@lifescienceconnect.com

Tim Bretz / 724-940-7555 / Ext. 123
tim.bretz@lifescienceconnect.com

Cory Coleman / 724-940-7555 / Ext. 125
cory.coleman@lifescienceconnect.com

Scott Moren / Ext. 118
scott.moren@lifescienceconnect.com

Denise Mosley / 724-940-7555 / Ext. 126
denise.mosley@lifescienceconnect.com

Shannon Primavere / Ext. 279
shannon.primavere@lifescienceconnect.com

Perry Rearick / Ext. 263
perry.rearick@lifescienceconnect.com

Ray Sherman / Ext. 335
ray.sherman@lifescienceconnect.com

Tracy Tasker / Ext. 297
tracy.tasker@lifescienceconnect.com

Derek Van Slyke / Ext. 217
derek.vanslyke@lifescienceconnect.com

Casey Weed / Ext. 219
casey.weed@lifescienceconnect.com

DATA ANALYTICS
Rick Miller
rick.miller@lifescienceconnect.com

Kevin Morey
kevin.morey@lifescienceconnect.com

PRODUCTION DIRECTOR
Lynn Netkowicz / Ext. 205
lynn.netkowicz@jamesonpublishing.com

amri

Complex Science. Expert Solutions.

WE'VE GOT IT DOWN TO AN EXACT SCIENCE

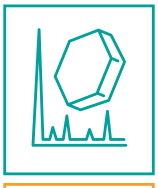
AT EVERY STAGE, AMRI DELIVERS THE EXPERTISE YOU NEED.

Discovery

Harness the power of broad target class coverage, state-of-the-art technology and expertise in multiple disease areas for comprehensive drug discovery.

Development

Advance compound development and gain strategic insight into manufacturability through our rapid, robust solutions.

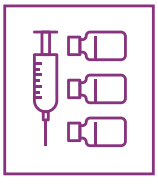


Analytical and Solid State Services

Speed product development and improve the quality of your compound with solid state chemistry and analytical testing services.

API Manufacturing

Power API production with global, cost-effective commercial manufacturing of your niche and high-barrier-to-entry compounds and a growing catalog of more than 240 APIs.



Drug Product

Optimize the path of your product at any point from compound to commercialization through our expertise in complex, sterile development and manufacturing.

Explore our expert solutions at amriglobal.com

North America • Europe • Asia | 1.518.512.2000 | www.amriglobal.com

ASK THE BOARD

Have a response to our experts' answers? Send us an email to rob.wright@lifescienceconnect.com.

Q How will the biopharma and services industry evolve over the next 5 years?

A BIOPHARMA FACTORY SALES are expected to grow about 20 percent faster than GDP growth. Some other changes include:

- R&D spending will grow at about a 3 percent CAGR, while spending on R&D outsourced services will grow 4 percent per year.
- More "killer experiments" will be conducted to reduce the current high cost of developing new drugs. These experiments will use better predictive tests, and the use of genomics, biomarkers, EMRs, claims data, patient stratification, and Bayesian statistics will become more common.
- CROs, CDMOs, and CMOs will have better access to data and data analytics. Their margins will gradually rise as lower-margin smaller players are weeded out.

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 How can I foster a culture of innovation?

A TO QUICKLY CATAPULT INNOVATION:

1. Share the vision and provide context. Engage and inspire your organization by helping them understand what's at stake: Why is innovation so important to us (or the patient/consumer/customer)? What will innovation help us achieve? And what's the cost of doing nothing?
2. Invite new thinking. Genuinely welcome creativity and embrace unconventional approaches. Interact with bright minds within, and beyond, the walls of your organization. Encourage dialogue that goes beyond the here and now.
3. Give people room to create. Protect free time on everyone's calendars for undisrupted strategic reflection, imaginative thought, collaborative brainstorming, and experimentation.

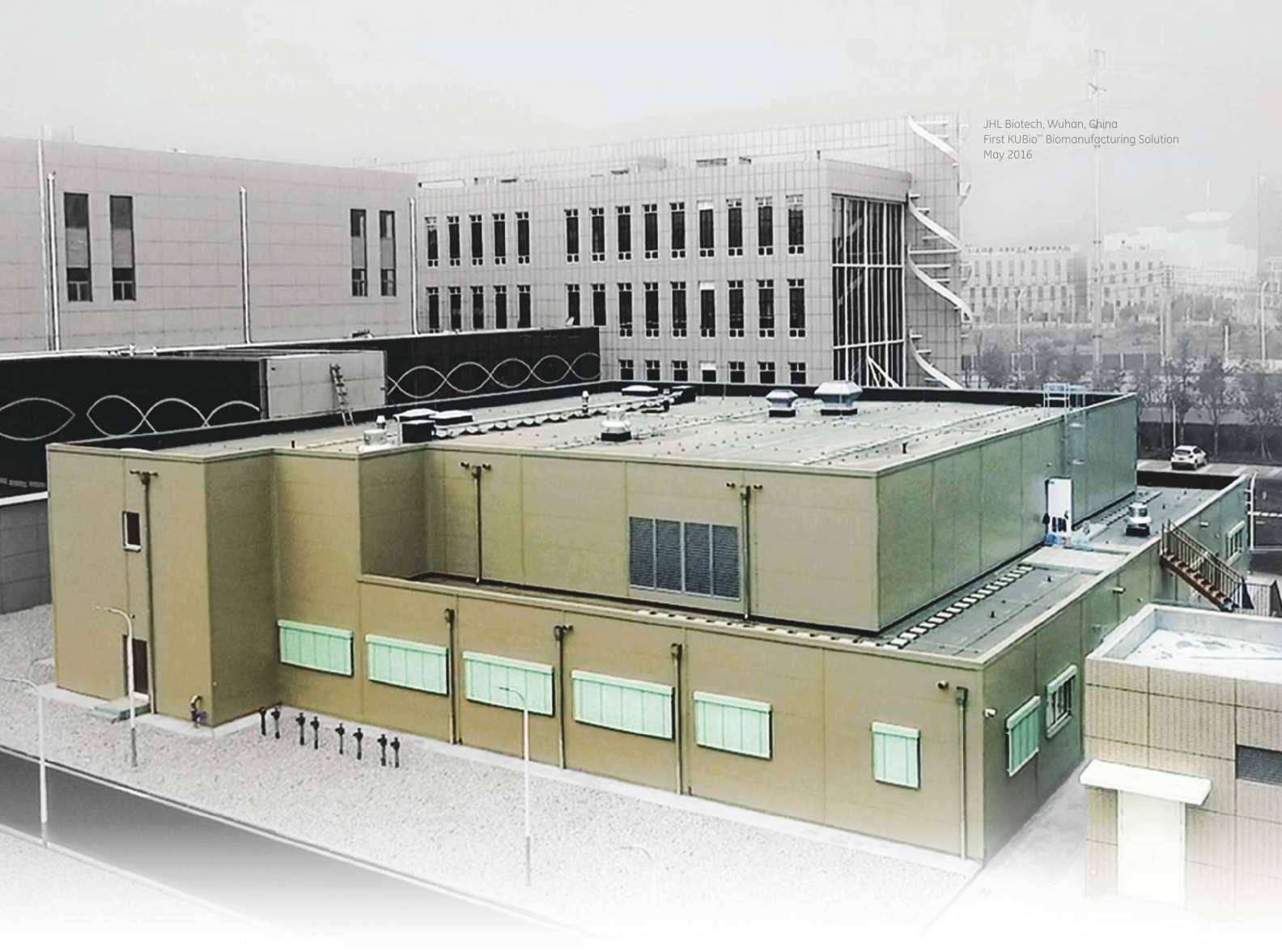
LIZ BYWATER, PH.D.
is a leadership expert, popular speaker, and author of the forthcoming *Slow Down to Speed Up!* She helps top executives drive growth, propel innovation, and lead change.

Q What do you see as the cause of declining R&D productivity?

A R&D productivity in decline is a questionable assumption. Productivity should be measured by the development of investigational new drugs rather than how many get approved. On average, developing a new drug takes 10 to 15 years and costs $2.6 billion. A big contributor to this cost is attrition (i.e., five in 5,000 investigational drugs ever make it to human testing, and only one of those ultimately gets approved). Other contributing factors include the shift in investment priorities from acute to chronic, intractable, and degenerative diseases; increased regulatory burden on authorities; increased need for research to meet payer demands; increased focus on areas where science is difficult and failure rates high; and increased trial complexity.

Improving R&D efficiency requires transforming the clinical trial process by utilizing adaptive clinical trial designs, incorporating Big Data, building strategic alliances, and integrating comprehensive partnerships that include patients, payers, government research agencies, healthcare providers, and contract service organizations.

MITCHELL KATZ, PH.D.
has 30 years' experience in the pharmaceutical and biotechnology industries, including preclinical research, pharmaceutical operations, and regulatory affairs. He is the Head of Clinical Research and Drug Safety Operations at Purdue Pharma L.P.



JHL Biotech, Wuhan, China
First KUBio™ Biomanufacturing Solution
May 2016

Transform biomanufacturing

Whether launching a new molecule for the first time, bringing biosimilars to emerging markets, or moving toward commercial manufacturing, GE's Enterprise Solutions provides you with real options at every stage of biomanufacturing. With renewed flexibility, speed and efficiency, we help you extend the availability of quality biologics to regions where they are needed most.

Apply a range of comprehensive solutions including a fully functional facility, flexible single-use platform, integrated automation and a suite of tailored services to accelerate your bioprocessing journey.

gelifesciences.com/enterprise

GE Healthcare Bio-Sciences AB, Björkgatan 30, 751 84 Uppsala, Sweden.

29215294 AA 03/2017

ProMIS Neurosciences

Targeting toxic forms of beta amyloid and other misfolded proteins that cause neurodegenerative diseases such as Alzheimer's and ALS

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

ProMIS Neurosciences is in preclinical development of monoclonal antibodies (mAbs) targeting the toxic oligomers of proteins, such as amyloid beta, that cause neuron death in Alzheimer's and amyotrophic lateral sclerosis (ALS). In parallel, ProMIS is creating companion diagnostics to match agents targeting specific prions to appropriate patients.

WHAT'S AT STAKE

If you have a guided missile, be careful where you aim it. In medicine, the closest thing to an ICBM is the monoclonal antibody and its descendants, the various molecular scaffolds for delivering drugs to all the right places. People forget or never learned that mAbs almost died an early death, the first products exploding on the launch pad. Not for lack of power, but for lack of accuracy.

But the issue of targeting remains in each new use of mAbs for treating diseases whose causes are still unknown or inadequately understood. ProMIS believes inaccurate targeting is to blame, in fact, for lack of progress against Alzheimer's disease, as marked by the headlined failure of Lilly's solanezumab last year. "Neurodegenerative diseases are caused by the toxic oligomer variants of misfolded proteins, like beta amyloid or tau, not the monomer or plaque forms of beta amyloid — that's the key insight," says Gene Williams, executive chairman. "What we know now is the neuron-killing variant is the toxic oligomer. Amyloid monomer is created in your brain from the moment you're born; it's a breakdown product of the amyloid precursor protein. The only pathological role of the monomer is that it aggregates; it is the raw material for making toxic oligomers."

In youth, the immune system continually clears the beta-amyloid monomer or plaque from the brain, but under stress or age, the system may fail to keep up, and the plaque accumulates, he explains. Yet the manifestation of Alzheimer's disease in the mass death of neurons is not caused by the plaque, he asserts, but by toxic, misfolded oligomers of the beta amyloid and tau proteins, or *prions*. "In Alzheimer's, the toxic oligomer of beta amyloid can interfere with tau through hyperphosphorylation, creating toxic tau, and it looks like both of the toxic oligomers are involved in killing neurons. But the key is, if you're treating the disease, you have to be highly selective for the toxic oligomer form."

Biogen/Neurimmune's aducanumab, the first Alzheimer's drug to show cognitive improvement, has a dose ceiling because it causes a side effect called ARIA (amyloid related imaging abnormalities), which involves fluid leakage from the blood into the brain. Williams accredits the effect to insufficiently narrow targeting and believes his company's approach will improve on therapeutic accuracy.

ProMIS actually screens a large number of different mAbs for their ability to bind with the unique "epitope" of the targeted oligomer, the part of the receptor on the surface of the beta-amyloid prion cells to which an antibody will attach. Drawing on the considerable experience and expertise among its leadership and staff, it has created preclinical models and other tools for dissecting the toxic prions involved in Alzheimer's and ALS.

So far, the company's proof of concept has played out precisely. In fact, with multiple therapeutic candidates identified, it also hopes to apply even more "precision" to its medicine with its companion diagnostics, which would match treatments aimed at different epitopes to patients whose pathologies involve particular toxic oligomers. It is natural to wonder whether clinical trials will only clarify the value of individual testing or perhaps render it moot if a single prion type proves overwhelmingly critical in causing disease.

GENE WILLIAMS
Executive Chairman

Vital Statistics

15
Employees

Headquarters
Toronto, Ontario

Finances

Total Raised
$7.7M
CDN raised in four private placements

Toronto Stock Exchange
ProMIS is publicly traded on the TSX.

Latest Updates

May 2017:
Company identifies novel therapeutic epitope target for ALS and dementia.

July 2017:
Company-sponsored research agreement with University of British Columbia receives matching grant from Canadian Institutes of Health Research.

In addition to the subject-matter experts he interviews for his feature articles, Chief Editor Rob Wright is constantly networking with biopharma executives at top industry trade shows and via site visits. In addition, he frequently reaches out to subscribers to gauge their opinions on what's hot in this ever-changing industry. Here are some recent unsolicited emails he's received.

Hi Rob,

I enjoy your biographical articles about the career paths followed by various biotech executives. I also enjoy the articles by prominent biotech R&D leaders about the strategies being pursued by their R&D divisions. I often share your stories about the paths that various biotech leaders followed throughout their careers.

J., SANOFI GENZYME

Hey Rob,

I enjoyed the Vivek ["What's The Backbone Of Vivek Ramaswamy's Success?"] article, per usual; good stuff and neat to learn about their onboarding (opt in/out) process.

C., GENZUM LIFE SCIENCES

Rob,

I found your May 2017 issue to be excellent, not only because of the continued highlighting of CEOs (love the idea of an issue about retired CEOs) but also the John McManus article on consolidation of providers and also the very interesting Cuban Biopharma trend, Part 1.

M., BIOGEN

Rob,

Congrats again on another fine publication — it's one that I anticipate with enthusiasm all the time. I truly enjoy the information, and I also value the entertaining insights that you often collect through your interviews.

R., MERCK

Dear Rob,

I found ["Journey To The Corporate Boardroom"] to be a very useful and insightful article. I may never serve on a board myself, but it was quite interesting to see how one goes about it.

S., NOVARTIS

Dear Rob,

I'm writing to express how much I value your CMO Leadership Awards issue. Life Science Leader has become an invaluable resource for me to find worthwhile news and information, frequently from the industry leaders and experts directly via interviews and awards, as well as diversified columns. We used the award issue to help us understand the landscape and the type of services that all the different companies are providing.

O., ATRIN PHARMACEUTICALS

340B Reform Gets A Kick Start

JOHN MCMANUS The McManus Group

In a swift one-two punch, potential reform of the 340B drug discount program suddenly lurched into gear when:

1. The Energy & Commerce Committee held an oversight hearing, with newly installed Chairman Greg Walden (R-OR) citing concerns with the "340B program's rapid growth without additional and proportional oversight;" and
2. The Trump administration released a proposed rule to reduce Medicare payments for Part B drugs to 340B hospitals from average sales price (ASP) +6 percent to ASP -22.5 percent.

BACKGROUND

The 340B program was enacted in 1992 to give safety-net hospitals assistance with prescription drugs for their indigent and uninsured patients. It provides statutorily mandated discounts of 23 to 100 percent (depending on the drug and how it has been priced from date of launch).

In testimony to the Energy & Commerce Committee, the Government Accountability Office (GAO) observed, 340B hospitals "can purchase drugs at 340B prices for all eligible patients regardless of the patients' income or insurance status and generate revenue, such as by receiving reimbursement from a patient's insurance, that may exceed the 340B price paid for the drugs. The 340B program does not dictate how covered entities should use this revenue or require that discounts on the drugs be passed on to patients."

The size and scope of the program has ballooned in recent years — more than doubling from nearly $6 billion in 2010 to more than $13 billion in 2015 and is projected to keep growing for the foreseeable future, according to Berkeley Research Group. The GAO noted that the number of covered entities — hospital sites and grantees — had more than doubled in the past five years, totaling 38,000 sites in 2017.

Erin Bliss, assistant inspector general for evaluation and inspections at HHS Office of Inspector General, testified, "Despite the 340B program's goal of increasing access and providing more comprehensive care, neither the 340B statute nor HRSA guidance speaks to how 340B providers must use savings from the program — nor do they stipulate that the discounted 340B price must be passed on to uninsured patients."

That is a remarkable statement. The Office of Inspector General (OIG) admits the 340B drug discount program may not actually lower drug costs for patients and does not know what the providers are doing with these substantial resources!

When Chairman Walden pressed Capt. Krista M. Pedley, director, office of pharmacy affairs at HRSA, if the agency knows how the savings are spent and whether patients are benefitting, she responded, "The statute is silent as to how savings are used. Therefore, HRSA does not audit or have access to that information." Sounds like we are in need of statutory reform!

The skyrocketing number of "contract pharmacies" is also troubling — growing from 1,300 in 2010 to 18,700 in 2017, making the prospect of illegal drug diversion to patients unrelated to the 340B hospital much more likely. While 340B providers are prohibited by law from dispensing 340B-purchased drugs to anyone who is not their patient, the law does not define what constitutes a "patient." How is it then enforceable? Moreover, if the only sanction is paying back what you stole, where is the deterrent?

Chairman Walden acknowledged that HRSA has made improvements to its oversight efforts, but HRSA's audit activities remain at or below 200 annual audits

of covered entities since 2012 despite the rapid growth of the 340B program.

Though the congressional hearing is an excellent way to spark interest in the issues, the hospital lobby is powerful and should not be underestimated when it comes to actually trying to move legislation. While 340B hospitals are spread across every member's district, drug companies are located in a select few ZIP codes.

340B HOSPITAL OUTPATIENT PROPOSED RULE

Concerned with congressional inaction on 340B but committed to advancing reforms, the Trump administration released a proposed rule that would reduce Part B reimbursement for 340B drugs to ASP (average sales price) minus 22.5 percent. The thought is that Medicare should benefit from the discounting in the 340B program, not just allow hospitals to profit from the spread between the 340B price and the current reimbursement scheme of ASP plus 6 percent. These ideas have been circulating from MedPAC (Medicare Payment Advisory Commission), GAO, and the OIG for several years, but the industry was surprised when the Trump administration issued the proposal in the heat of the drug-pricing debate.

The CMS proposal would save Medicare $900 million in lower payments for Part B drugs dispensed by 340B hospitals, including $180 million in lower copayments by beneficiaries. Yet because the hospital outpatient payment system is budget neutral, those cuts would result in commensurate increased spending on other items and services. That quirk in the law is another reason a legislative solution is required — unrelated services, such as imaging and outpatient surgery should not receive payment increases simply because Medicare pays acquisition cost for HOPPS (Hospital Outpatient Prospective Payment System) drugs at 340B hospitals.

Notwithstanding the hoopla over the CMS proposal, a proposed rule does not necessarily mean it will become finalized policy. Hospital groups quickly mobilized to oppose the proposal, with the American Hospital Association urging CMS to "abandon its misguided 340B proposal and instead take direct action to halt the unchecked, unsustainable increases in the cost of drugs."

Hospitals that participate in 340B must be deemed "nonprofit" hospitals, which do not pay taxes because of the "community benefit" they provide. But in mid-July *Politico* — the inside Hill rag read by most Capitol Hill aides — released a devastating critique of the so-called nonprofit hospital sector. Its investigation showed the top seven hospitals by revenue (all deemed nonprofit) substantially increased their revenue under Obamacare, but simultaneously dramatically cut their charity giving. Operating revenue jumped from $29.4 billion in 2013 (before ACA implementation) to $33.9 billion in 2015 (the last year data is available). In that same period, the free treatment for low-income patients by those hospitals plummeted from $414 million in 2013 to $272 million in 2015.

Politico explains: "To put that another way: The top seven hospitals' combined revenue went up by $4.5 billion after the ACA's coverage expansions kicked in, a 15 percent jump in two years. Meanwhile, their charity care — already less than 2 percent of revenue — fell by almost $150 million, a 35 percent plunge over the same period."

Not a single hospital has lost its tax exemption despite massive profits, which are often spent on executive salaries, elaborate new facilities, and provider acquisitions to strengthen market power.

This is not to say that the entire hospital industry is faring well. According to a recent Chartis Group and iVantage Health Analytics study, 41 percent of rural hospitals faced negative operating margins in 2016. And since 2010, 80 such hospitals closed. There are a variety of reasons, including serving the disproportionately sick, lack of a necessary supply of physicians, and low volume of patients.

But perhaps it is time to rethink the concept of community hospitals. Hospitals that exploit a drug discount program designed to assist low-income beneficiaries and are thriving on various government-run payment schemes ought not be able to escape the taxation required of all other businesses in the U.S. Just as important, new and innovative ways of delivering care should be explored, particularly in rural and underserved areas. For example, freestanding emergency centers essentially constitute the first floor of a hospital and can provide vital emergency care in underserved areas, yet Medicare does not recognize them as legitimate providers. Providing more accessible care at a discount seems like a workable solution.

The momentum is with proponents of reform to hospital payments and the 340B program. Now is the time for action! 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.

Collaborating To Stem The Tide Of Emerging Antimicrobial Resistance

JEFFREY STEIN, PH.D.

Before the first antibiotic, penicillin, became widely available, we lived in a primitive age of medicine. The only cure for an infection prior to the mid-1940s was luck. While antibiotics have prevented many needless deaths over the last several decades, we are now at a tipping point where infections are once again gaining the upper hand.

Overuse and misuse of cheap, generic antibiotics and antifungals over time has created the noxious problem of disease resistance. The CDC reports, for example, that widespread usage of antifungals in the azole class has stimulated an increase in azole-resistant strains of *Candida*. This is only one example of a number of new and emerging strains of drug-resistant pathogens that can cause severe and often deadly infections, such as bloodstream infections and pneumonia. These "superbugs" easily thwart available medicines and can spread rapidly within a population. Once a patient contracts an infection from one of these superbugs, death can be swift in the absence of effective treatment.

There's been ample news coverage in the last year about the emergence of a virulent fungal infection called *Candida auris*, which has been identified in more than 120 patients in the United States and linked to four hospital deaths. What's particularly worrisome is that *Candida auris* in some cases has shown resistance to all three major classes of antifungals available to treat invasive fungal infections.

Given the innovations in modern medicine, it is hard to believe that an estimated 23,000 people in the United States die yearly from drug-resistant bacterial infections; around 2 million people are infected overall. Fungal infections are associated with even higher mortality with nearly 1.8 million hospitalized patients and 97,000 attributable deaths per year in the U.S. Collectively, these infections incur healthcare costs of $21 to $34 billion annually.

Globally, there are at least 700,000 people who die each year as a result of antimicrobial resistance (AMR), which includes bacteria, viruses, and fungi. The WHO, for the first time, recently published a list of 12 drug-resistant pathogens, with three deemed "critical" in terms of risks to humans. The "critical" group includes multidrug-resistant bacteria that pose a particular threat to patients in hospitals, nursing homes, or under certain kinds of treatment.

WHAT WE CAN DO NOW

It's time we identify aggressive solutions to AMR, and it will require a combination of strategies. We'll always encounter drug-resistant pathogens, yet I'm confident that through collaborative, multidisciplinary approaches, we can stem the tide of this alarming trend.

Nurses and doctors need more education and guidance around prescribing of antimicrobials. Healthcare facilities need better diagnostic capabilities to catch the signs of infection earlier in the game and ensure that the right drugs are prescribed. Organizations should invest in antibiotic stewardship programs to ensure the appropriate use of antimicrobials. The latter can lead to better patient outcomes and a reduction in the spread of drug-resistant infections.

From my vantage point, streamlining the path for bringing new drugs to market is a top priority. We need to push hard on this endeavor, given the time it takes for new medicines to gain FDA approval and reach their intended audiences.

RESOLVING MARKET BARRIERS FOR NEW DRUG DEVELOPMENT

The climate for anti-infective drug development over the last decade has been generally unfavorable: Less than 5 percent of pharmaceutical investment goes toward antimicrobial development. The last new class of antifungals was introduced in 2001, and no new antifungal agents have been approved for *Candida* bloodstream infection since 2007. More than ever, we need rapid innovation in new antimicrobials, yet today, only a handful of large pharmaceutical companies are still in this market.

The main barrier is a dearth in economic incentives for researchers and drug companies to invest time and money into the process. Strict and complicated regulations in this country make it difficult to finance the development of anti-infectives, when factoring in the cost, complexity, and high risks of the clinical trial process. Adding to the problem, the return on investment of antimicrobials is not enticing. Antimicrobials are not intended for frequent use by a large market, but for sparing application in the case of serious infections.

Yet there has been some progress. On the legislative front, the 21st Century Cures Act aims to facilitate a faster approval pathway for antibacterial and antifungal drugs that treat a serious infection in a "limited population of patients with unmet needs." The law requires that drug manufacturers include disclaimers on drug labels stating that the newly approved antibiotics are for a limited population, which may help to prevent misuse or overuse of these therapies. The 2012 Generating Antibiotic Incentives Now (GAIN) Act also provides fast-track FDA review and extended market exclusivity for qualified new antibiotics.

COMBATTING AMR REQUIRES COLLABORATION

I am a big believer in collaboration to address market barriers and find tangible solutions to combat this serious public health issue. That's why I'm involved with the Antimicrobials Working Group (AWG), an industry-led coalition of emerging antimicrobials companies committed to improving the regulatory, investment, and commercial environment for antimicrobial drug development. AWG's priorities include encouraging greater flexibility in regulatory approval requirements for new drug development, while exploring alternative pricing and reimbursement models to support a robust antimicrobials pipeline.

Since AWG's founding in 2012, we have had notable success working with government officials, as well as other stakeholders such as the Infectious Diseases Society of America (IDSA), the CDC, and BIO in refining legislative proposals designed to improve the environment for companies developing drugs to address AMR. These accomplishments include playing an instrumental role in the GAIN and 21st Century Cures Acts.

Another exciting collaboration, launched in 2016, is CARB-X — the world's largest public-private partnership of government, industry trade groups, charitable foundations, and life science accelerators created to battle antibiotic-resistant bacteria. The organization invests in promising, early-stage projects to accelerate development with the intent to build a diverse portfolio of at least 20 new antibiotic products.

The United Nations is also getting involved, through the recent establishment of an Interagency Coordination Group on Antimicrobial Resistance, which is designed to provide practical guidance on how to address AMR and coordinate global efforts. The group will support governments across the world and advise on the appropriate use of antibiotics.

Lastly, in 2013 the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH, established the Antibacterial Resistance Leadership Group (ARLG). To date, the ARLG has reviewed more than 70 study proposals and initiated more than 30 clinical studies, which include designs to optimize enrollment and testing in therapeutic trials and methods to improve clinical trial efficiencies.

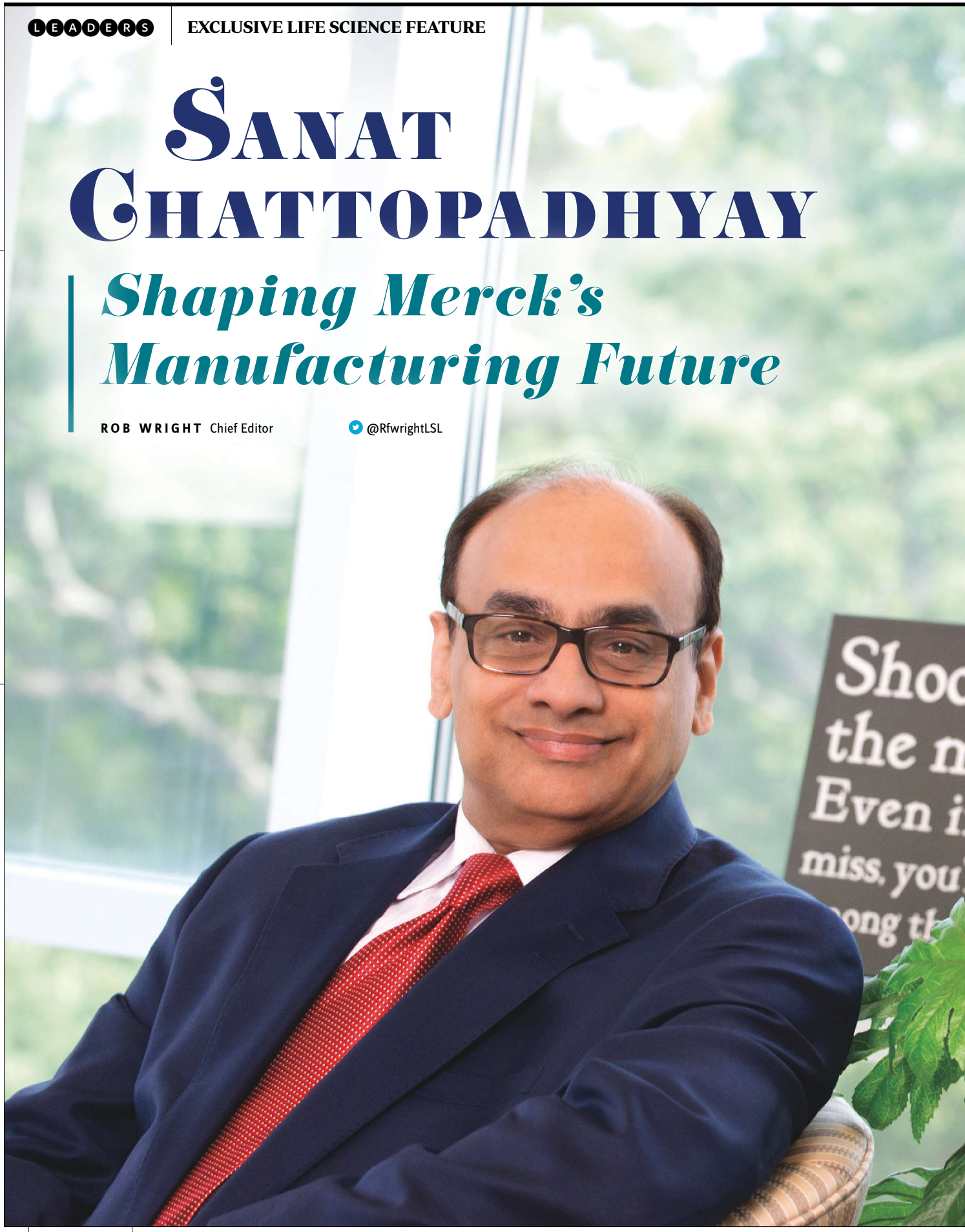
These are all commendable initiatives, yet there's still a lot more work required to bring new antimicrobials to market. Resistance to antimicrobials is predicted to reach tsunami proportions, yet the pipeline is practically dry. If we don't make progress soon toward battling superbugs and suppressing development of new ones, resistant infections could kill more than 10 million people per year globally by 2050. That number is far higher than deaths from cancer, diabetes, traffic accidents, and other current leading causes of mortality. Let's not wait any longer — anyone can get involved, from physicians, nurses, and researchers to entrepreneurs and policymakers. The time for action is now. L

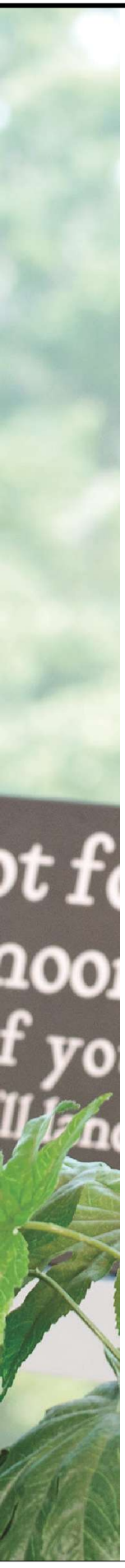
JEFFREY STEIN, PH.D., is president and CEO of Cidara Therapeutics and chairman of the Antimicrobials Working Group (AWG).

SANAT CHATTOPADHYAY

Shaping Merck's Manufacturing Future

ROB WRIGHT Chief Editor @RfwrightLSL





Sanat Chattopadhyay knows what it is like to face difficult tasks in the biopharma industry. When he was just 30 years old he was tapped to be the CEO of a small, wholly owned subsidiary of Hoechst Pharmaceuticals, India, engaged in manufacturing and selling of semi-synthetic beta lactum antibiotics. The company wasn't doing well, but he was expected to create something that he would be asked for over and over during his future career — a transformational turnaround.

"To return the company to profitable growth in the shortest period of time, I knew that I needed a new team," he recollects. "But with the current state of the company, it was difficult to motivate and recruit more talented leaders. I quickly learned the importance of earning the confidence of others, and I gained a deep understanding of the value of humility."

Fast forward to April 2016 when Chattopadhyay was named president of Merck* Manufacturing Division (MMD) and an EVP on the Big Pharma's executive committee. He's learned a lot in between that first CEO job and now, and we were lucky to sit down with him to hear some of the stories that have shaped him as a leader and prepared him for his current transformational turnaround challenge — reshaping MMD to be ready for its biopharmaceutical manufacturing future.

With Every Challenge Comes A New Lesson Learned

While still at Hoechst, Chattopadhyay experienced a series of mergers and company restructurings (i.e., Hoechst Roussel merger with Marion Merrell Dow, which later merged with Rhône-Poulenc Rorer to form Aventis, and eventually Sanofi). While at Hoechst Marion Roussel, as the head of Indian subcontinent manufacturing operations, he had the opportunity to restructure the company's manufacturing footprint which consisted of five sites and about 4,500 employees. Oh, and do so while reducing costs and improving gross margins.

"We ended up closing most of the sites, reduced the workforce by 70 percent, and radically expanded our external manufacturing capabilities," he recalls. In addition to contracting with about 50 CMOs, Chattopadhyay says the company also embarked on building a new greenfield manufacturing site. It was a complex and stressful experience that further honed his leadership chops — especially in terms of talent management. "I also learned how to negotiate with a very aggressive unionized workforce."

In his next position as head of manufacturing operations at Aventis Europe, he learned an important tenet of biopharmaceutical manufacturing leadership. "Senior manufacturing leaders should not only solve problems when they occur, but be able to sniff out the glitches before they happen," he says. "Very often, supply is interrupted by a variety of technical issues in quality and compliance or in process and analytical robustness." The better a leader is at doing Failure Mode Effect Analysis (FMEA) of business operations, the better they will be at understanding the single points of failure — and the less likely they will be surprised by unexpected manufacturing interruptions. "One of the best ways for manufacturing leaders to help their organizations is to become champions of the unsung 'fire prevention' heroes."

Understanding Manufacturing's Role

Those past positions led to him being hired at Wyeth where, after a few years, he was put in charge of transforming the company's commercialization organization. Although this experience was similar to those past projects, he calls it "a defining moment" in his career.

"In a research-driven pharmaceutical company, it is clear that the R&D enterprise creates value by building a company's pipeline," he states. "Marketing enhances that value by building brand equity through market penetration and expansion. I didn't fully understand either of these concepts until I was at Wyeth." With this challenge, he earned a much deeper understanding of the role played by each of a company's organizations/divisions and how they need to work together. He even earned greater insight into his own discipline. "Manufacturing's role is all about value preservation," he explains. "Ensuring the best manufacturing quality, compliance, and supply at a competitive cost prevents disrupting and eroding all the value and trust created by the R&D and marketing sides of the business."

*MSD outside the U.S. and Canada

A Difficult Balancing Act

According to Chattopadhyay, failure rates are extremely high for small molecule products to make it all the way to approval. "You have to be very careful about how you invest in manufacturing capabilities because if it is too much too early and the product fails, the write-off could be very high." Conversely, sometimes between Phases 1 and 3 there can be a dramatic acceleration of timelines resulting from very positive data readouts. Receiving a breakthrough therapy designation from FDA with accelerated approval timelines requires having a very speedy product launch capability.

While at Wyeth, to deal with such a balancing act, Chattopadhyay tried a few things. First, they tried to outsource post-Phase 2b process development activities to variabilize costs along with establishment of in vitro/in vivo correlation to develop and optimize drug formulations. Then they focused on solid-phase chemistry, namely crystallization, in order to create the right particle size that allowed for the most forgiving formulation designs for broader specification for dissolution. Such approaches helped to improve agility and speed with developing process and analytical robustness for the launch of new small molecule products.

Merck Vaccines — A Lesson Learned The Hard Way

When Chattopadhyay was hired by Merck in November 2009, he was given the challenge of transforming vaccine manufacturing and supply. Success in the previous few years, namely the launch of four new vaccines (i.e., GARDASIL, RotaTeq, ProQuad, and ZOSTAVAX) had made Merck the largest vaccine company in 2007. But the overnight success also created a gap between its value creation (i.e., R&D) and value preservation engines (i.e., manufacturing). That gap had caused a succession of technical problems. From 2007 through 2010 the company experienced frequent supply interruptions and prolonged stock-outs of its vaccines, which was reflected in the FDA's drug shortage listing. There were recalls (i.e., 1.2 million doses of pediatric

How Will Biopharmaceutical Manufacturing Evolve?

In the last 10 years there has been tremendous focus in Big Pharma on restructuring. "Companies were primarily looking to reduce the size of their manufacturing footprint with an outcome of reducing the conversion cost," explains Sanat Chattopadhyay, president of the Merck Manufacturing Division (MMD). "The conversion cost is basically the value-added cost." Thus, if a company reduces the number of its internal manufacturing sites, it reduces the number of people, thereby lowering its conversion cost and improves the network capacity utilization. "Whether it's product life cycle management, improving a product's gross margin, enabling speed to market, or any of the things that can make a meaningful improvement in profitable growth, the biopharmaceutical world has been captivated by the thesis of attacking primarily the conversion cost, which is best achieved through outsourcing and/or low-cost country sourcing."

Chattopadhyay believes this trend resulted from companies not looking for other ways to reduce cost of goods sold. By closing down a few manufacturing sites, companies were able to not only reduce their fixed costs, but convert some of what was left to a variable cost via outsourcing. "But we didn't pause, think, and explore what companies in other industries were doing to try to reduce costs," Chattopadhyay says. "A manufactured pharmaceutical tablet is essentially 80 percent material cost and only 20 percent conversion cost, on an end-to-end basis. Why are we so focused on attacking the smaller of the two percentages?" He feels biopharmaceutical companies need to consider deploying new technology platforms, innovation in manufacturing and analytical processes, and other means (single-use technology, etc.) by which they can reduce the 80 percent material cost and radically improve gross margins. "In biologics, there are examples of companies creating massive plants only to end up mothballing them for many years because the company was able to increase the yield of a manufacturing process so astronomically that they were able to be much more efficient on a much smaller manufacturing footprint." With cell lines capable of yielding >40 gms/lts titer, one can try to grow the cell mass continuously and crystallize the antibodies also continuously to drastically reduce the cost of monoclonal antibodies to < $10/gm, for both small and large volumes, depending on whether it is an acute care or a chronic therapy product – that is the kind of future the pharma industry should gear up to create.

While it is more common to have such surprises in biologic processes, Chattopadhyay feels companies should not ignore trying to make process improvements in small molecule manufacturing. He is not alone. Frank Gupton, Ph.D., a former pharmaceutical manufacturing

vaccines) and numerous supply interruptions for its shingles vaccine ZOSTAVAX.

At all of those previous companies, Chattopadhyay noticed that much of the success for those transformation projects depended on talent management, talent recruitment, and team creation. And at Merck he knew there was a tremendous amount of preexisting technical talent. "What we lacked was a few leaders with deep vaccine manufacturing operations experience," he says. "So, while I built on the great foundation given by my predecessor, most importantly I also hired some enormously talented leaders and tasked them with getting the best from the people we already had."

The leaders were given some autonomy on how to best achieve the goals of the initiative, and one manager opted to use the book *QBQ! The Question Behind the Question: Practicing Personal Accountability at Work and in Life* by John Miller. The book was used to help communicate Chattopadhyay's leadership philosophy of personal accountability. At Merck's Pennsylvania West Point vaccine manufacturing facility, at least 400 copies were distributed to team members. "By the end of 2012, we had a very different face, and all of the vaccine shortages had practically vanished from the FDA website," Chattopadhyay concludes.

He says 99 percent of the Merck vaccine and manufacturing operations talent remained unchanged during the transformation. So, there was no need to "slash and burn" to achieve success of this magnitude. "The new leaders were great at reminding everyone after the transformation not to give credit to the newcomers, but to congratulate those doing the work," he explains. "After all, these were the same people who had done the work in the past, only now they were reporting to new leaders."

Avoiding The Manufacturing Challenges Of The Past

Like many of the iconic pharma companies that have traditionally focused on small molecule drugs, Merck is becoming more biologically focused (e.g., KEYTRUDA). As such, it's up to Chattopadhyay to make sure MMD's biologic manufacturing capabilities don't suffer from the same challenges that affected its vaccines division.

executive turned professor at Virginia Commonwealth University (VCU), has been exploring how to do this very thing through the Medicines for All Initiative (M4All), a project supported by the Bill and Melinda Gates Foundation and the Clinton Health Access Initiative (CHAI). According to Gupton, the cost of producing a wide range of pharmaceutical products is higher than it needs to be, particularly in the area of APIs, which make up 60 to 70 percent of a drug's cost. But the initiative is also looking at reducing costs in starting materials and pharmaceutical manufacturing processes. Thus far the project has achieved dramatic yield improvements, waste minimizations, and cost reductions for three high-volume HIV drugs.

Outside of Gupton's work, Chattopadhyay believes the focus on product and process improvement tends to be much more prevalent in countries such as China and India. "In the United States, we are too intoxicated with the concept of reducing the conversion cost via outsourcing," he says. "I expect this trend to change as people realize the limitations of this as a means of reducing the conversion cost." Since a huge amount of the site closures have already happened, companies will be looking for other means to reduce costs.

Questions being explored at MMD to reduce material and manufacturing costs (i.e., non-conversion costs) include:

- Is there a way for us to redefine MMD's starting materials?
- Is there a way for us to reduce the total number of synthesis steps?
- Is there a way for us to reduce the input per unit output and improve yield?
- Can we create standard technology platforms so the cost base becomes much different, regardless of the product's life cycle?
- Can we achieve high levels of quality and compliance with lower levels of investment (i.e., standardization)?

"Many of the concepts we are investigating (e.g., combinations of lean capabilities, novel ways of looking at technology platforms, adaptive formulation, and filling technologies) will not only enable speed and flexibility at low cost, but become commonplace in industry," Chattopadhyay affirms. "The advanced analytics are getting leveraged a lot more to improve production yield and reliability." As such, Chattopadhyay expects the following manufacturing support areas to experience significant growth: rapid micro methods, sterility testing, mass spectroscopy (MS), Raman spectrometry, nano screening, ultra-performance liquid chromatography (UPLC) for extended characterization of biologics, and various raw-materials screening devices. "The manufacturing industry of pharma will look a lot different in the future, as the concepts of miniaturization, continuous manufacturing, and single-use systems (SUS) become commonplace," he concludes.

If Merck R&D continues to deliver results, Chattopadhyay believes MMD can ensure access to these therapies only if it achieves the following:

- Has the highest quality at the lowest cost, with the shortest lead times
- Is a top quartile performer in cost of goods sold, working capital, and compliance
- Is an industrial leader in speed to market with flawless new product launches
- Has a best-in-class talent reservoir.

"This is our manufacture-the-future model, which was previewed in October 2015 and then formally rolled out in October 2016," he shares. The strategy is all about compliance, supply, profit plan, and people — four elements that should remain constant for nearly every biopharmaceutical company's manufacturing division.

The Five Pillars of MMD's Strategy

There are five pillars of Chattopadhyay's MMD transformation strategy: stability, responsiveness, innovation, biologics, and talent diversity. "For me, stability is number one because we want to have the mindset of safety first and quality always, which go hand in hand. As a pharmaceutical manufacturer, if you cannot guarantee the safety of your employees or the quality of the product to the consumer, then you should be in another business," he advises.

Stability

MMD is aiming for very high standards of compliance, including top-quartile performance in on-time-in-full (OTIF) and line-item-fill-rate (LIFR) greater than 98 to 99 percent, right-first-time of 85 to 95 percent, with zero market actions and zero safety incidents. In 2015, the division installed a "Safe by Choice" program to build accountability, conviction, and commitment into every MMD employee. "We're creating extreme vigilance and remediation in high-risk areas (e.g., hazardous energy, spillage of solvents, confined areas)," he explains. "A focus on safety will create a very high right-first-time attitude, minimize recalls, redefine inspection excellence, and improve customer service."

Responsiveness

MMD is striving to be in the top quartile in terms of cost of goods sold and inventory. "To do this we need to become much more agile, which will be evidenced by end-to-end lead-time reduction," he states. "As for speed to market, we will have to be enormously good at this because we are looking at a large number of potential breakthrough therapies in the pipeline, and you cannot underestimate the advantage of being the early mover."

Innovation

Chattopadhyay expects technology platforms to change dramatically in the future and continuous manufacturing to become more pervasive. "The future will belong to small, agile, and modular formulation facilities that can produce four times more volume at a fraction of existing setup and changeover times — and do so for even one batch." He believes such changes will crash direct costs and lead times while also changing the competitive field, especially the difference in capital and conversion cost between the western economies and India and China.

Biologics

This pillar has its roots in the highly successful clinical trials for KEYTRUDA in 2012. The company needed to create a robust manufacturing process for a monoclonal antibody in lyophilized formulation in less than 24 months — "which was a huge challenge for Merck," Chattopadhyay notes. Still, the product was successfully launched in 2014 and is expected to generate between $6 and $8 billion by the year 2020. "In KEYTRUDA we have more than 500 clinical trials in 32 different tumors with more than 60 mono and combo therapies involving more than 8,500 patients. That's why biologics is an MMD strategic pillar."

Talent Diversity

Shifting MMD toward a biologics culture requires a new kind of mindset that is focused on developing a long-term biologics network. "For example, we are working on mammalian cell culture and striving to develop high-titer product that can get produced in single-use systems (SUS) in a modular format so we can continuously grow the cell mass very high and continuously crystallize those antibodies," Chattopadhyay explains. "To do all this we need to change the paradigms of talent diversity at MMD, not just skill diversity, but gender and generational diversity as well."

Like any seasoned biopharma industry veteran, Chattopadhyay knows his days of facing seemingly insurmountable challenges are far from over. This is a fickle and constantly changing industry where transformational turnarounds are inevitable. Luckily for Merck, with Chattopadhyay at the helm of this $40 billion enterprise, they have a leader who is not only up for the challenge, but also well prepared for it. L

emergent
biosolutions®

BDS Manufacture | Single-use Platform | Aseptic Fill/Finish | Vials & Syringes | Clinical & Commercial

Protected.

Everyone wants to be protected. With Emergent BioSolutions, you can be sure you are. They have a proven track record as a quality provider of contract manufacturing services, for both bulk drug substances and sterile injectable drug products. They are dedicated to one simple mission: to protect and enhance life.

See how Emergent protects lives.

50
PROTECTING & ENHANCING
50 MILLION LIVES BY 2025

ebsi.com/CMO
800-441-4225 | CMO@ebsi.com

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

CHASING INVENTION

JEFFREY KINDLER AT THE HELM OF CENTREXION

Sometimes, this industry creates problems only it can solve. The current opioid epidemic — aka, America's new war on drugs — offers a case in point. If prescription opioids can be lumped together with street drugs such as heroin and fentanyl as a cause of addiction and death, the only logical solution is to withdraw them from the market. If attempts to create abuse-deterrent forms of the prescription narcotics have backfired, let's abolish the concept of chronic pain and give the drugs only to dying patients in the most extreme agony. Or when patients cut off from the meds still insist on whining about their condition, let's offer them the alternative of switching to a lifelong neuropsychiatric drug that, even if it fails to relieve their pain, at least makes them less depressed about it. Or, better yet, maybe someone should just go back to the drawing board and do what the best of the industry does — invent a better drug.

That someone — or some company — may be Centrexion, now led by the former chairman and CEO of Pfizer, Jeffrey Kindler. Centrexion is developing novel

agents to relieve some of the worst chronic pain experienced by human beings, without causing addiction or the other adverse effects of opioid medicine.

Hold on, someone who ran a top-five Big Pharma is now heading a biopharma startup? Perhaps the picture is not so unlikely. At his former company, a behemoth formed through many mergers, Kindler dealt with the frustrating conundrum of ballooning R&D budgets tracking alongside plunging R&D productivity. Coming from another discipline and a different industry — he was the head legal executive for McDonald's and head of litigation and policy at GE — he had joined pharma just as the leading consolidated companies struggled to operate at a much greater scale. Now, at Centrexion, he exemplifies a more recent trend: enlistment of former top executives from the industry's largest companies to manage some of the smallest. Still, from Kindler's vantage point, his career has always turned toward new opportunity, and it has taken him where R&D is actually creating something needed and new — a pure enterprise, chasing invention.

"I had spent my career in very large organizations, and I was really attracted to the opportunity to be involved in a startup environment and its very different culture. I became an adviser and investor in a lot of such companies, and still am, and then the opportunity to get involved in Centrexion presented itself," he explains.

A DIFFERENCE IN PAIN

Like many biopharma executives, however, Kindler had a personal motivation for taking command of a startup. His wife suffers from osteoarthritis, a condition that causes endless, intractable pain for millions of patients. Not even the infamous opioids offer much help with arthritic pain.

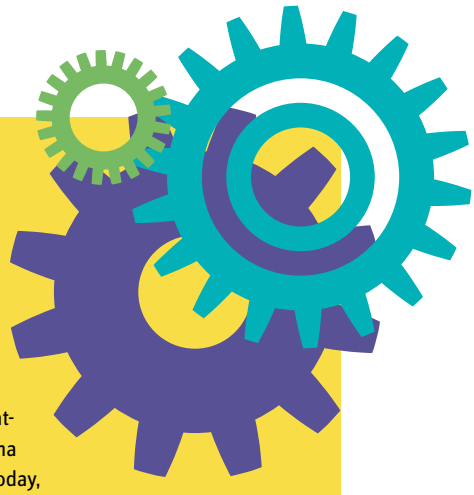
"The treatments available today are really inadequate in a lot of ways, whether they be over-the-counter drugs or prescription agents that have various adverse cardiovascular or GI effects; steroids, which have a limited ability to treat over time before they start to produce tissue damage; hyaluronic acid injections, which are not particularly effective; and ultimately interventions such as knee surgery," he says. "With the opioid crisis, there's just a tremendous need for alternatives. Centrexion is addressing an enormous medical need in a very compelling way, and it was a chance to apply some of the things I had learned and experienced at Pfizer to a new environment."

Kindler says he didn't fully appreciate the scope of the pain problem until he became more involved in the area.

THE SCIENCE-BUSINESS CROSSROAD

BIOPHARMA COMPANIES FORM AND OPERATE AT THE INTERSECTION OF SCIENCE AND BUSINESS. HOW MUCH SHOULD THE CEO OF SUCH A COMPANY KNOW ABOUT ITS SCIENCE, AND HOW MUCH SHOULD ITS SCIENTISTS KNOW ABOUT THE BUSINESS OF THE COMPANY AND THE BUSINESS CHALLENGES IT FACES? JEFFREY KINDLER, WHO HAS RUN A BIG PHARMA AND NOW HEADS THE BIOPHARMA STARTUP CENTREXION, ANSWERS:

"In one of my other activities, I'm partnering with Roch Doliveux, the former CEO of UCB, to mentor executives in healthcare through the GLG Institute. One of our programs helps scientists become better business people and business people become more conversant in science. In biopharmaceuticals, it's really important for each of those disciplines to understand the other. I'm not a scientist, but I do feel that I have to understand enough about the science and how it works so that I can make some judgments and decisions – and maybe even more importantly – be able to explain it and articulate it to the public and investors. I'm never going to be a expert on science, but my responsibility is to make sure we're employing people who are really great at it. I need to know enough to be able to talk to the scientist and evaluate for myself whether their judgments are sound. Conversely, the scientists have to understand that they're not there just to engage in science experiments, but that we are a business that is trying to create value for not just our patients but our investors, and they have to have some appreciation for how all that works."



BEST MODEL FOR INVENTION?

HAS SO-CALLED INNOVATION, IN THE BROADEST SENSE, SHIFTED MAINLY TO THE SHOULDERS OF SMALLER COMPANIES, FROM THE LARGER ONES? JEFFREY KINDLER, FORMER BIG PHARMA TOP EXEC AND NOW CEO OF THE STARTUP CENTREXION, IS NOT READY TO MAKE THAT CONCLUSION. KINDLER SAYS NO SINGLE BUSINESS MODEL CAN COVER EVERY OPPORTUNITY OR CHALLENGE.

"We have tremendous advances in science, an enormous need for more cost-effective prevention and treatment, and a very complex healthcare system. The days are gone when any one business model, Big Pharma or something else, could address all these problems in an effective way on its own. What we have today, emerging and getting better all the time, is a collaborative ecosystem where all the different models – academia, the government, Big Pharma, specialty pharma, biotechs – all have their role to play and increasingly need to work together.

"There was a time in the 1930s and '40s when each Hollywood studio had everything under one roof, and they churned out movies, and they didn't really require any kind of collaboration or partnership. Today the studios put together movies with partnerships and contracted players. I think that's what's emerging today in biopharma. Big Pharma has a very important role to play. It has scale and resources that smaller companies don't have. It has the ability to commercialize, especially in larger therapeutic areas in ways that small companies can't. It's able to take a lot of risks because of the diversity of assets that it has. But smaller biotech companies like ours can bring real focus and attention to particular areas that sometimes are harder to achieve in a large organization. There is an important role for both of them to play, and it's just that much more important that everybody work together in a collaborative ecosystem.

"It is interesting to see how many former Big Pharma CEOs like myself, Jeremy Levin, Deborah Dunsire, or Chris Viehbacher, have gone on to running smaller biotechs. There is nothing as effective in understanding the healthcare system as working at a large company like Pfizer, which participates in so many different therapeutic areas and engages around the world with so many different players in the healthcare system. It is an incredibly valuable set of experiences and is really hard to duplicate in a small company. The experience and the knowledge that I gained about how the healthcare system works and the role pharmaceuticals play in it is of great value to us as we advance our company, and I wouldn't trade that experience for anything. But it is a lot of fun now to be in a situation where I can have a much more personal and direct impact on what we're doing. At Centrexion, we have a fantastic team, but it's a very small team, and I'm very personally engaged in what's happening in a direct way that I could not do at Pfizer."

He points out that the 100 million people in the United States who suffer chronic pain at some point in their lives amount to a larger population than for cardiovascular disease, diabetes, and cancer put together — and pain-related disability claims cost billions of dollars. Of course, misuse of prescription opioid drugs could add much more in costs to the total. No one can say at this point how much actual relief a potent, nonaddictive alternative would bring to the problem; opioids will not lose their appeal for "extratherapeutic" users. But as opioids vanish from all but the most extraordinary practices, a nonaddictive option could offer patients safer pain relief from the beginning of treatment on.

Centrexion is ready to enter Phase 3 development with its lead drug, coded CNTX-4975, for treatment of knee-osteoarthritis pain and has a pipeline of other candidates and indications moving in parallel or following behind. CNTX-4975 and the other agents inhibit the transmission of pain signals to the brain. Development is focusing initially on localized pain; CNTX-4975 uses the company's STRATI (Synthetic TRans cApsaicin ulTra-pure Injection) technology, which addresses the previously enormous challenge of administering a drug based on capsaicin, the "hot" ingredient of hot chilies.

Past attempts at developing capsaicin-based drugs have run up against the burning sensation they create when administered, which can cause acute, though transitory, pain to a patient. Kindler says Centrexion has taken years to work out a pretreatment procedure that contains the numbing agent lidocaine and involves controlled cooling, taking the sting out of the injection treatment.

The program illustrates a lesson from his experience in Big Pharma — spend time to perfect a compound, formulation, and delivery that improves on treatments in the existing standard of care. Although the search for a solution to the administration challenge began before his arrival, Kindler was well-prepared to appreciate the value of such development in potential ROI.

Any company developing treatments for patient-reported symptoms can take another lesson from Centrexion's experience: Develop drug candidates that yield unequivocal results, based on how they act in the body. Corollary: When possible, avoid entirely the effects that make the current treatment standard unsatisfactory.

"Doing clinical trials for pain can be challenging because you ultimately depend on the patient's subjective view of whether their pain has improved, and often a placebo effect makes it difficult to prove the efficacy of the medication," Kindler says. "Even more complicating, opioids trigger the pleasure sensations in the brain that create addiction. But our technology doesn't work that way. Our drug is a very selective agent, interrupting the local pain signal. It has a very short half-life and is out of the body in 24 hours. It affects only the local pain nerves and has no activity outside of them. If our Phase 2 results are repeated in Phase 3, our drug will be a profound game changer that allows patients to visit the doctor only twice a year, get an injection, and experience very significant pain relief with no meaningful side effects."

Unlike opioids, Centrexion's product will not be a scheduled drug, which would require patients to sign a contract with the prescribing physicians and take periodic drug tests. "It will not be scheduled because it has no addictive or dependency issues whatsoever. Based on the evidence today, it's as safe as a placebo," says Kindler.

So, is it more effective than placebo — or rather, the infamous placebo effect? That turns out to be a challenge on its own. The placebo effect has typically run high in pain trials because patients tend to anticipate relief, especially when injected. Centrexion's chief medical officer, Dr. Randall Stevens, has introduced some clinical trial measures — including careful training of investigators and patients — that help separate the placebo and drug effects significantly, as seen in the Phase 2b results, according to Kindler.

"It is considered a good result in pain trials if 50 percent of the patients experience 50-percent reduction in pain," he says. "In our Phase 2b trial, nearly two-thirds experienced a 70-percent reduction, and about a quarter of the patients experienced at least a 90-percent reduction. Our patients are coming in having failed other treatments and having a pain score in the 6 to 10 range, or moderate to severe pain, and after the treatment they're down to 3 or less, which is mild or no pain. That's a really meaningful change in someone's life and how they go about their daily activities."

Other Phase 3-ready programs for CNTX-4975 include a treatment for osteoarthritis in pet dogs and an orphan condition of Morton's neuroma, which was granted FDA fast-track review status. The condition causes extremely painful neuromas to form between the toes. It is especially prevalent among women who wear high heels and marathon runners. The only current treatment is surgical removal of the neuromas, which creates numbness and often leads to eventual relapses.

SINGLE FIELD, FULL PIPE

Another possible lesson from Centrexion, Kindler, and perhaps the Big Pharma world: If you want to broaden your pipeline, minimize risk by expanding indications for the same compound or similar ones from the same platform. The company has generally followed that pattern, but it also has shown its willingness to act opportunistically rather than stick to its in-house STRATI technology. It has purchased three assets from Boehringer Ingelheim: a CCR2 (chemokine receptor 2) antagonist for inflammatory pain, a CB2 (cannabinoid receptor) agonist for neuropathic pain, and an SSTR4 (somatostatin receptor 4) agonist for various potential chronic pain indications. The company also acted in a wholly practical fashion with its lidocaine gel product to fill a gap in treating areas of the body, such as the face, where lidocaine patches work poorly or not at all.

"Each of these is either a first-in-class or best-in-class asset, or both, that is in Phase 1 studies and that we intend to advance," says Kindler. In early research, Centrexion's chief scientific officer, Dr. James Campbell, is working on "intrathecal" (spinal-column) delivery of pain medicines for the most severe kinds of pain. "We are developing injectables, small molecules, oral drugs, topicals, and intrathecal drugs. And, we are using many different kinds of delivery systems, but what they all have in common is that they are effective, safe, nonaddictive treatments for chronic pain."

Rather than try to replace the standard, first-line treatments right off the bat, the company is developing its products for patients who have already tried and failed all standard options, from opiates to OTCs to neurologic drugs such as Cymbalta or Lyrica. The subtext lesson here is develop your product to improve on standard care but avoid challenging Goliath until you've beaten lesser foes. But Kindler leaves no doubt about Centrexion's ultimate aims: "The company we're building here will answer an enormous medical need for the hundreds of millions of people around the world who suffer from pain every day — chronic pain that affects their lives in terrible ways." In the rapidly upending world of chronic pain, nothing could be more welcome.

IPSEN IN THE USA — BUILDING & LEADING THE SUBSIDIARY AS STARTUP

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

Cynthia Schwalm, president, North American commercial operations for Ipsen, heads a historic initiative by a company few people on the west side of the Atlantic have ever heard of. It all started about three years ago when the company decided to take a literal leap and go where it had only stealthily gone before — into North America, with the United States as the primary goal.

Previously, outside of the U.S., Paris-based Ipsen had both specialty care and primary care businesses. It had conducted some basic R&D at a facility in Massachusetts and acquired several small biopharma companies that enabled it to be commercially active in the U.S. since 2009.

But Schwalm says the company's focus shifted to specialty and biotech starting in 2012 with the overall goal of becoming a truly global specialty biopharma company. "The trajectory of the company changed when we decided to actively research, develop, and market biotech specialty products in the United States instead of just being a partner to others."

By 2013, Ipsen had completed a "worldwide landmark registration trial" on Somatuline Depot (lanreotide) for neuroendocrine cancer, an indication estimated to be worth almost $1 billion in the United States. "When the trial data was delivered and published in the New England Journal of Medicine, that was the tipping point for the company to make its bid for the $800 million U.S. market," she says.

A QUICK START FOR A NEW LEADER

To spearhead this U.S. initiative, the decision was made to bring in a new team based in a new Basking Ridge, NJ, headquarters. Schwalm was asked to lead that team.

Their primary task was to launch the company's position in oncology and drive its position in neuroscience and other rare diseases. Only five months after Schwalm joined the company, the FDA approved Somatuline Depot for treatment of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Things continued to move quickly when, in 2015, she began overseeing the R&D Center in Massachusetts and — possibly more impressively — created a Canadian satellite (now employing about 30).

"Ipsen had never been in Canada therapeutically," Schwalm explains. "I actually had set up a Canadian operation prior to this for another company, so I knew how important it was to understand all of the differences between the two countries, from clinical development to health outcome, pricing policy, and launch processes. The classic mistake I've seen companies do is just to send Americans or Europeans into Canada, but Canada is not

DRUG PRICING & KEEPING INNOVATION IN THE U.S.

Some companies in the specialty space also have led much of the debate over drug pricing – and not, in the most notable cases, by good example. Like most industry veterans, Ipsen's top U.S. executive Cynthia Schwalm sees such overriding "external" issues as vital concerns for every biopharma company, and she has particular views based on her long experience.

"The sad part is looking at how the majority of the industry has not governed itself in pricing, but I think we are starting to see a tipping point," she says. "The large American-based pharmaceutical companies are self-reporting what they plan to do with their pricing policy, which is a first. Also, PhRMA is starting to regulate its membership and ensuring that membership is based on companies that are putting at least 10 percent of their revenue back into innovative R&D."

Schwalm also reserves some advice for the public sector: "I'm hopeful that we'll continue to see some traction toward keeping the innovation and our people and our tax base here." She recalls the former program of federal tax breaks for pharma companies that built factories in Puerto Rico as an example of effective but unfortunately abandoned policy. She believes close-to-home manufacturing also can keep companies innovative.

"We acquired not only the rights but the manufacturing facility for ONIVYDE from Merrimack, and it's located right in Cambridge. ONIVYDE is a very difficult product to make, and we are also making some of the experimental medicines there that Merrimack kept. It is our intent to keep that manufacturing process in the United States, which may be unusual now, but it's all part of innovation, especially in biotech, keeping that special capability close to the market."

In time, more industry voices may join Schwalm and others in balancing the public debate over healthcare policy, company behavior, and innovation. Meanwhile, she will likely continue to prove her own worth as effectively the CEO of Ipsen's U.S. startup. Her leadership and the company's performance to date have already made their marks.

the United States or Europe; it is the tenth largest market in the world, and it's unique, so it deserves due respect." As such, she adds that Ipsen's locations in the two North American countries operate distinctly.

> **"WE CAN GO DOWN IN THE RECORD BOOKS AS ONE OF THE FASTEST ONCOLOGY STARTUPS IN RECENT HISTORY."**
>
> **CYNTHIA SCHWALM**
> President, North American Commercial Operations, Ipsen

This year, Ipsen purchased the oncology assets of Merrimack Pharmaceuticals, led by a U.S.-marketed product, ONIVYDE (irinotecan liposome injection), for metastatic pancreatic cancer. And recently Schwalm was put in charge of a new manufacturing site in Cambridge, MA. In all, the U.S. organization has about 300 employees.

She emphasizes the already-positive effects of Ipsen's North American landing. "Our stock price has increased on average by about 50 percent per year since early 2015 when we launched an oncology organization in the United States, and our shareholder return has increased more than 153 percent. With those kinds of metrics, we're now starting to catch the attention of U.S.-based investors. So, we're gaining momentum. We can go down in the record books as one of the fastest oncology startups in recent history."

EXPLORER AND BUILDER

In the European custom of prosaic executive ranking, Schwalm's title downplays her responsibilities; she is more like an American CEO, building and heading a new company subsidiary with its own focus and portfolio — in oncology, neuroscience, and rare diseases. She manages the "legal entities" of Ipsen in North America (the United States and Canada) in an organization that is effectively an operating company. She also carries a worldwide EVP title, reflecting her membership in the company's worldwide operating committee.

Schwalm came into this industry more than 30 years ago from her initial career in medicine, starting as an oncology and critical care nurse with ambitions to become a physician. While she was studying to take entry exams to medical school, she received a job offer to be a medical device sales rep. She took the job and found she enjoyed it so much she decided to continue her career on the industry side. Soon, she was recruited to be one of the first 50 founding sales representatives for Janssen Pharmaceutical.

"I've always maintained positions where I could stay extremely close to the patient agenda. That is what drew me into the biotech and specialty settings, and it's what has kept me in the specialty setting." To help master business management along with her desire to help patients, Schwalm later earned an Executive MBA from The Wharton School.

Since embarking on the industry course, she has managed multiple businesses globally working in Europe, Asia, and Latin America. From J&J's Janssen and Ortho Biotech, she went on to run oncology at Amgen, serve as president of Eisai U.S., and work as an adviser to biotech and specialty companies for two years, before joining Ipsen.

MOMENTUM BEYOND ONCOLOGY

These days, any oncology startup will likely face the question of whether or how its portfolio might include immunotherapy. Ipsen has already licensed, tested, and abandoned a Phase 3 immuno-oncology candidate

RECENT MILESTONES

JUNE 30, 2017
Dysport copromotion agreement with Saol Therapeutics to expand commercial reach in the United States

JUNE 16, 2017
FDA approval of Dysport for the treatment of lower-limb spasticity in adults

APRIL 3, 2017
Completed acquisition of ONIVYDE and additional oncology assets from Merrimack Pharmaceuticals

JANUARY 9, 2017
Ipsen to acquire oncology assets from Merrimack Pharmaceuticals

AUGUST 1, 2016
FDA approval of Dysport for the treatment of lower-limb spasticity in pediatric patients aged two and older

WOMEN AT C-LEVEL = WIN FOR EVERYONE

It is a simple fact that Cynthia Schwalm, who heads the U.S. startup company of Paris-based Ipsen, is a woman who has succeeded as an executive in an industry traditionally dominated by men. We asked her to discuss what her experience has been and what it means for women of her generation, as well as the next one, in their ongoing struggle to rise to equal participation at the highest levels of industry leadership.

SCHWALM: In the early years, when I was in my early 30s, I started to drive down the career path of becoming a general manager, with P&L responsibility. One of the issues women faced at that time – and still do – is the trade-off of work and family. I've been happily married for 31 years, I have two bright, beautiful daughters who are 23 and 24, and I had the good fortune of being able to travel through my life journey with the right leaders who didn't penalize me for wanting to be a mother or saying no to a certain job at a certain time because I needed to do a certain thing. A greater opening is coming, when people can actively navigate their lives within their profession, but it has to come for young women and young men alike. I am hopeful that the day is coming when they can feel fully self-expressed with their families, even taking care of elders, and still choose the right job and be open to relocation at the right time. Unfortunately, the statistics still show that there is not only a glass ceiling, but a cement ceiling for C-suite females. Research shows that boards and companies do better when there's more than one woman at the table, and that's just good business sense. Given that women are over half the world's population and are the majority purchasers of healthcare, one would argue that the focus needs to continue on the work toward diversity. I do not subscribe to the statement that there aren't enough good women to do the job; there are. I happen to be an example, and I've been around for a while. I have been a member of the John F. Kennedy School of Government women's leadership advisory board for almost eight years, and their systematic research shows how efforts to include women in the leadership agenda actually are better for society and for business.

but is still looking for other IO opportunities for itself or with partners.

But although Ipsen's new U.S. arm is a self-identified oncology startup, it brings a few nononcology assets over from the parent company. First among them is Dysport, the biologic forming a "therapeutic" and "aesthetic" product line rivaling Botox and marketed for more than 20 years only outside the United States. In 2010, Ipsen's exclusive global commercial partner for Dysport, Nestle-owned Galderma, won FDA approval for the product in treating cervical dystonia, a rare neurological condition. Since then, Ipsen U.S. has gained additional approvals for the product in treating adult spasticity, as well as childhood spasticity primarily related to cerebral palsy.

Dysport has received three therapeutic FDA approvals in less than two years and has just received approval in cervical dystonia in Canada. This past June was a milestone month, in which Dysport became the only botulinum toxin approved by the FDA for the treatment of spasticity in adults in upper and lower limbs and for the treatment of lower-limb spasticity in children ages two and older. It also has a Phase 3 clinical trial moving toward an expected registration in pediatric upper-limb spasticity during the next two years. The company recently announced a Dysport copromotion agreement with Saol Therapeutics to expand its commercial reach.

Galderma continues to market the Dysport aesthetics line globally, leaving Ipsen free to focus on therapeutic forms of the product. "Dysport is part of Galderma's whole aesthetic portfolio, which covers the entire landscape from medical spas to plastic surgeons, so it's a natural fit for them to market Dysport," Schwalm explains. "We focus on pediatric neurologists, adult movement-disorder doctors, and adult and pediatric physical medicine and rehabilitation. Those are very different commercial models."

Dysport's competitive advantage in aesthetic and therapeutic uses alike seems to be its extended duration of benefit, Schwalm stresses. "As confirmed by all of our experience and data on the product, at least 20 percent of the patient population experiences a benefit from the therapy for over three months at a time. That is a distinguishing feature of Dysport, though it plays out differently in the therapeutics, aesthetics, pediatric, and adult populations."

Today, the U.S. division is the number-one affiliate for the Ipsen Group. "The U.S. division has gone from being 4 percent of Ipsen's worldwide revenue in 2013 to more than 20 percent currently, and it is now the innovation engine and commercial engine for the company," says Schwalm. "A primary initiative for us this year — and going forward — is to help the rest of the markets in the United States and Canada understand all of the company's capabilities."

Gaining Recognition For A Novel Portfolio – Deal By Deal

MICHAEL GOODMAN Contributing Writer @MikeGoodma

After an impressive series of deals with big and midsize pharmas, Pieris Pharmaceuticals finds itself at an inflection point, close to several important data releases and, if all goes well, to signing a partner for its most advanced candidate.

Founded in Freising, Germany, in 2001 as a spinoff from the Technical University of Munich, Pieris emerged with rights to an antibody-like protein technology called anticalins and with backing from a syndicate of European investors. Stephen Yoder took over as CEO in 2010 after an eight-year stint at MorphoSys serving as head of IP, general counsel, and later as head of out licensing. In 2015 the company moved its headquarters to Boston and completed an IPO on the NASDAQ.

Anticalins are basically a new therapeutic modality. Derived from endogenous human proteins called lipocalins, they differ from antibodies in being eight times smaller and of considerably less molecular weight. These and other structural properties permit them to be formulated for inhaled delivery or as a sustained-release depot. They are nonimmunogenic, can easily be formatted in bispecific and multispecific constructs, provide superior tissue penetration, and can be produced in bacterial cells at lower cost than antibodies. In short, their human origin makes them safer and their physical properties enable them to bind not only larger proteins but also targets previously considered too small for other protein approaches, including hapten-like targets and small molecules.

BALANCING INNOVATION AND EXECUTION

Yoder comes across as crisp and thoughtful for a 41-year-old, first-time CEO. When he started at Pieris, his mandate was quite different from what it is now. "We were backed by rather fatigued European VCs who needed an exit because their funds were aging and their LPs (limited partners) were calling." The idea back then was to close a few deals, validate the technology, pay the bills, and, with luck, repay his investors with a trade sale.

But he found that selling an early-stage platform company was challenging. Yoder chalks that plan up to being green. So he and his team decided to build the company for long-term value, to invest in disease biology that might unlock key benefits of anticalins where antibodies would have a high barrier to entry. After a lot of soul searching, he settled on the idea of targeted co-stim. In immuno-oncology (IO), T-cell co-stimulation through agonist receptors (e.g., OX40, GITR, 4-1BB) is an extremely active area of R&D where co-stim agonist antibodies are combined with antagonist checkpoint antibodies (e.g., PD-1 or CTLA-4). Co-stim antibodies are believed to promote the expansion and proliferation of killer CD8 and helper CD4 T cells — types of white blood cells that lead the attack against infections.

Yoder realized that "Industry is not buying platforms, they're buying drugs." So he refocused Pieris on immunology, beginning with IO, and on a pipeline based on co-stim anticalins — for now, 4-1BB — paired with antibodies hitting validated targets and on multispecific constructs (e.g., tri-specifics, tetra-specifics). Yoder stresses, "We're not probing novel biology; rather we address known targets in new ways." Nonetheless, Pieris has joined the leading rank of companies working with alternative antibody scaffolds (e.g., Molecular

Partners' DARPins, Amgen/Micromet's BiTE antibodies, Ablynx' nanobodies).

That's the innovation side of the company.

How Pieris goes about lining up partnerships to advance its pipeline of bi- and multi-specific anticalins is the execution part. It requires the discipline to limit the portfolio to the IO and autoimmune respiratory categories, the smarts to know which ideas to invest in, and the patience and assets to lure the right partners to the negotiating table.

It also calls for the flexibility to know that no business strategy is written in stone; rather, strategy evolves as the science, policy, and competitive dynamics change.

A STEADY STREAM OF PARTNERS

Over the past seven years, Pieris has executed a series of collaborations and partnerships that have progressed with respect to terms and economics, and have accelerated in the past two years. The company lists seven deals on its website dating back to 2010.

In fact, it also has inked collaborations with Takeda (2011) and Allergan (2009) in which it provided anticalin discovery expertise in return for a small up front. Extensive restructurings — Pieris was partnered with Takeda San Francisco; in 2012 the San Francisco campus closed and was consolidated with San Diego — scuttled the Takeda collaboration; and of the Allergan deal, Yoder says, following Allergan's hectic period of mergers and acquisitions, "It is the slowest diligent development of a molecule I've ever seen." He ascribes no value to it. The table below shows Pieris' current key partnerships.

The recent AstraZeneca partnership reflected Yoder's confidence coming off the Servier deal. He pushed hard for the terms, and he got them, signaling that he and his team were prepared to take PRS-060 to proof of concept on their own. He maintains that partnering '060 early allowed Pieris to lock in to the inhalation device that it would ultimately be commercialized in. "We don't have to make any bets about the device," he says, "and that accelerates time to market — real value for shareholders." Moreover, '060 would be able to enter the market at a lower dose and lower cost.

AstraZeneca is a world leader in formulation and devices for respiratory therapies — that helped to

PIERIS KEY DEALS 2013-2017

PARTNER	DATE	ECONOMICS & TERMS	DEAL FOCUS
AstraZeneca	May 2017	$45M up front; $2.1B in potential milestones. Pieris retains option to codevelop and copromote in U.S.	Global rights to PRS-060, a preclinical anticalin for asthma formulated for inhalation, up to four additional respiratory programs.
ASKA Pharmaceutical	Feb. 2017	$2.75M up front; potential $80M in option exercise fee and milestones. Pieris leads development to Phase 2A when ASKA can option. ASKA gets rights in Japan, South Korea, other Asian markets.	Deal focuses on Pieris' most advanced candidate PRS-080 to treat anemia in dialysis-dependent CKD patients.
Servier	Jan. 2017	$31.3M up front; $1.75B in potential milestones. Pieris retains option to codevelop and keep U.S. rights for four programs.	This is an IO deal. Servier gets PRS-332, a PD-1 based bispecific and four additional undisclosed molecules. The deal could be expanded to include additional programs.
Roche	Dec. 2015	$6.4M up front; $409.3M in R&D funding and milestones. Pieris is in charge of discovery tasks; Roche takes over at IND-enabling phase.	Deal focuses on an IO anticalin against an undisclosed Roche target. Agreement may be expanded to multiple targets.
Zydus Cadila	Oct. 2013	Payments undisclosed. Pieris discovers and takes junior role in early development of multiple anticalin programs. Pieris also retains marketing rights in key developed markets.	The most advanced candidate is PRS-110, a preclinical anticalin targeting cMET for unspecified tumors. Zydus retains rights in specific emerging markets.

de-risk the deal. So did the fact that '060 hits ILR4, the same target as Regeneron's dupilumab, which is approved for atopic eczema and in a pivotal trial for asthma; but where dupilumab is a subcutaneous injection, '060 will be inhaled.

ASKA was all about PRS-080 for anemia, a noncore asset in the new immunology-focused Pieris. Recent positive Phase 1 data raise the chances that ASKA will pay to option the drug at Phase 2A. ASKA is a small/midsize Japanese company.

Yoder says the Servier deal "was about doubling our footprint without sacrificing back-end economics." He met a number of objectives in his first big IO partnership: First, he wanted to hold onto his wholly owned IO asset PRS-343 — a 4-1BB targeting anticalin linked to a HER2 targeting antibody — for as long as possible. He also wanted to score a significant up front in order to extend the runway and bridge through some near-term clinical inflection points such as advancing PRS-343 through its Phase 1 multi-ascending dose trial (data available second half of 2018 [2H18]). Finally, he wanted commercial rights in the U.S. and the freedom to do additional IO partnerships.

Yoder sees ASKA and Servier as being much like Pieris — scrappy and hungry.

The Roche deal was all about validation. The industry's preeminent cancer powerhouse saw something in little Pieris' technology. It was a single target discovery collaboration, not much different from Daiichi or Sanofi, but with superior downstream economics. "It helped set the table for building our confidence and getting our name out in the industry," Yoder says.

Zydus is a slow-moving collaboration, the first deal where Pieris secured U.S. rights. "But it's not top of mind for us now."

Pieris' collaborations with Daiichi and Sanofi go back in time; their economics pale beside the more recent deals. Daiichi focused on two anticalin programs against in-house targets. One was against PCSK9. That market proved less attractive when the agent recently emerged from Phase 1, so Daiichi returned rights to Pieris, but it's still pursuing the second target. The Sanofi deal focuses on a tetra-specific anticalin against Pseudomonas aeruginosa pathogens.

The deals have brought in cash and recognition. In fact, the AstraZeneca deal doubled its share price. But Yoder recognizes that, ultimately, deals are not as validating as late-stage data. PRS-080 will be the first anticalin to report proof-of-concept data in humans. If the data proves out, Yoder looks forward to partnering it globally. And he is hoping that PRS-343, which recently started Phase 1, will post strong enough data to warrant accelerated approval.

With all these transactions, Pieris has managed to preserve a proprietary pipeline of IO candidates, in particular, its lead agent PRS-343. There are major compatibility issues with 4-1BB; Yoder cites Bristol-Myers' urelumab, which has shown some clinical activity, but its therapeutic window is small. PRS-343 "takes that potent co-stim biology at the tumor bed. And it's using HER2 as a magnet to recruit the immune system to tumors that aren't responding to HER2 treatments." Moreover, HER2 is expressed in multiple tumors, including those in the breast, bladder, and gastric areas.

The other proprietary IO program is PRS-342, a preclinical stage 4-1BB/GPC3 bispecific. GPC3, or glypican 3, is an oncofetal antigen with almost no expression in normal adult tissue. Its expression is pronounced in several tumors, including liver cancer, Merkel cell carcinoma, and melanoma.

Finally, Pieris is advancing a series of discovery-stage, multispecific anticalin fusion proteins.

A FLEXIBLE FUTURE

Pieris is committed to becoming a U.S.-focused company specializing in multispecific anticalins based on validated combinations of co-stim agonists linked to antibodies. For now it's pursuing low-hanging fruit in IO and immuno-respiratory. Yoder hints that the company sees opportunity in the broader autoimmunity space.

His team continues to push the discovery platform to produce new ideas because "We believe in building the pipeline of tomorrow and using it to drive additional partnerships in the future." He allows that Pieris may take on more target risk in the future, but for now he's playing it safe. The AstraZeneca deal has inspired the company to think hard about building out a proprietary respiratory franchise, and he and his team have been meeting with KOLs to become better acquainted with the space.

Yoder doesn't see other antibody specialists as competitors. "It's a big sandbox," he says, confident that Pieris has staked out a particularly fruitful area of biology.

The company is in a good spot. The Phase 2A study of PRS-080 should read out by early 2018; PRS-060 will enter Phase 1 in the second half of 2017; and PRS-343, the asset on which Pieris is betting its IO credibility, was about to recently start a P1 multi-ascending dose study, but FDA requested it modify the dose escalation part of the protocol. Pieris has responded to FDA's request and is awaiting word from the agency. Yoder still expects to report data in 2H18 and approval could be expedited if it wins breakthrough designation. An increasing number of analysts are covering the stock, too. Yoder is confident, finally, that investors are beginning to get Pieris' story. L

Automation and modularity allow mAb biotech to cut scale-up time

Original developers of biosolutions and products, especially those facing the debut of biosimilars in core markets, have an urgent imperative to reduce manufacturing costs via increased productivity and yields. To this end, bio-developers are adopting more sophisticated processes, such as perfusion, to address low titer cell lines and reduce raw material costs. They're also seeking more sophisticated and flexible R&D and PD capabilities by deploying equipment to enable simultaneous development of multiple products; automate rapid experimental design and implementation; optimize processes; and gain better analytical insights.

Introducing AlphaMab, a fully equipped bio-developer and producer

AlphaMab Co. Ltd, a fast-growing bio-developer and producer in China, is one such company looking for those capabilities. At AlphaMab, more than 100 scientists are engaged in a wide range of activities that include target validation, hit screening, H2L, PK/PD, pharmacology, cell line construction, process development, scale-up GMP manufacturing, and IND filing.

Scaling up production from lab to pilot to full commercial production raises many challenges — especially across many different projects. "The key difficulties are understanding the depth of process and the impact of parameters on process scale-up," said Dr. Ting Xu, CEO at AlphaMab. "These must be known in order to guide how we set our parameters for consistency during scale-up, so we can ensure cell growth, viability and yield and, ultimately, product quality."

AlphaMab has been an early adopter of single-use technology to help boost productivity in its cGMP manufacturing, while also reducing scale-up cycle times and costs. One complement to single-use technology is having a consistent automation platform across AlphaMab's different upstream and downstream phases, which the company defines using a Quality by Design (QbD) approach.

Finesse platform scalability and flexibility

In its cGMP facility, AlphaMab installed single-use Thermo Fisher Scientific HyPerforma bioreactors, each using a Finesse SmartSystem with G3Lite SmartControllers. The system consists of a control tower featuring Finesse transmitters and actuators, the latter controlling four mass flow controllers. "We chose the Thermo Fisher Scientific platform with Finesse G3 controllers because they offer proven performance, stability, and reliability, plus Finesse provides good service and support," said Xu.

What AlphaMab found unique about the Finesse G3 controllers is their versatile ability to scale-up and scale-down. "The scalability of the Finesse G3 control platform helps us facilitate process transfers from 0.5L to 2,000L," said Xu. "This enhances the quality, productivity, consistency, and reproducibility across our processes, whether we're using batch, fed-batch, or perfusion."

Another distinction is their adaptability to third-party systems and peripherals. For example, in addition to the Thermo Fisher Scientific bioreactors AlphaMab deployed, the Finesse G3 SmartControllers are compatible with single-use, glass, and rocker systems from Applikon, Sartorius, Eppendorf, Millipore, Xcellerex, CerCell, and GE. This enables customers to automate a wide range of both legacy and new-build infrastructure using what they determine to be best-of-breed solutions.

In combination with the Finesse G3 controllers, AlphaMab has found the Finesse TruBio® DV (DeltaV®) software extremely useful in controlling the bioprocesses of its cell culture operations. Finesse developed the hardware-independent software system based on the Emerson Process Management DeltaV control platform. "Having the DeltaV automation control engine in the TruBio DV software was an important factor in our selecting the Finesse automation platform," Xu said.

The cGMP-compliant TruBio DV software comes pre-configured with algorithms for controlling bioprocess parameters such as pH, dissolved oxygen, temperature, and pressure. With tridundant sensor loops as well as unlimited gas and liquid addition capability, the software can be used with glass vessels, wave rockers, and most brands of single-use bioreactors.

Executing scale-up standards for one project — or many projects simultaneously

"In the scale-up process, you have to find the key control parameters that affect your critical quality attributes, but each project has its own characteristics," Xu said. "The Finesse platform is a huge help in accelerating the technology transfer phases of our operations by enabling us to execute a scale-up standard across an entire project."

By migrating to single-use bioreactors while also automating with the same scale-up standards using the Finesse G3 SmartControllers and TruBio DV software, AlphaMab achieved two key goals: it reduced its scale-up cycle times to as little as 12 months, and it upheld its QbD standards, which ensure the quality of its process. The Finesse SmartSystem is also helping AlphaMab manage the scale-up and technology transfer of as many as 20 projects at a time.

For the complete article, please visit Finesse.com.

Finesse
part of Thermo Fisher Scientific

New Hampshire: A Biotech Microhub

CAMILLE MOJICA REY Contributing Writer

When it comes to ranking the nation's biggest biotech hubs, bragging rights go to places like the Greater Boston Area and the San Francisco Bay Area. Ask anyone living and commuting in these areas and you just might find that these hubs may be great for career options, but not so great for affordability and quality of life. As the biotech sector in the U.S. continues to grow, it is doing so not just in hubs, but in smaller places like New Hampshire — where some of the state's biopharma entrepreneurs say: "Smaller is better."

New Hampshire is home to 1.3 million people. Nearly 3.5 times as many people live in Greater Boston, which is less than an hour from the Manchester-Nashua area, one of the state's centers of biotech activity. The Granite State currently employs 7,000 people in its life sciences sector and is expected to grow by 8 percent by 2020 — a rate higher than the current 6.2 percent national growth rate, according to the NH Division of Economic Development's FY 16-17 strategic plan. Like most biotech hubs, New Hampshire owes its growing industry to the efforts of state and regional development agencies as well as research institutions churning out innovation.

Entrepreneurs are attracted to New Hampshire by the proximity to Boston, its relative affordability, the lack of sales and income taxes, and the bucolic charm for which the state is known. The state also has a range of business-friendly policies. In fact, *Entrepreneur* magazine currently ranks New Hampshire the second-best state in which to start a small business.

SMALL-SIZE ADVANTAGE

"The tax policy is the first thing people notice when looking to start or relocate companies here," says Jake Reder, CEO of Celdara Medical. Reder cofounded Lebanon, NH-based Celdara in 2008. The company has 16 employees, utilizes 50 to 60 contractors, and helps academic researchers all over the world commercialize their pharmaceutical discoveries. "A huge and often underappreciated advantage of living in New Hampshire is our small size. I know our elected representatives, and they know about Celdara Medical." New Hampshire Senator Jeanne Shaheen is the ranking member on the U.S. Senate Committee on Small Business and Entrepreneurship, while Senator Maggie Hassan sits on the Committees on Health, Education, Labor and Pensions, and Commerce, Science, and Transportation.

Reder also says there is truth to the local saying: "State government stays out of the way and out of our pockets." "It's an overly negative way of expressing another significant advantage of the mindset in New Hampshire." It's not that there isn't support for those entrepreneurs seeking assistance as they build their companies. A myriad of incubators, programs, and organizations offer help to young companies. Two examples are the NH Innovative Research Center located at the University of New Hampshire in Durham and the New Hampshire High Technology Council, the state's industry organization headquartered in Manchester.

New Hampshire already has several anchor life sciences companies, and is growing its own, as well. It is home to employees of several Big Pharmas, including Lonza Biologics and Novo Nordisk, both of which have manufacturing facilities in the state. In December 2016, the Department of Defense announced an $80 million award to Manchester-based Advanced Regenerative Manufacturing Institute (ARMI), a nonprofit organization focused on making the large-scale manufacturing of engineered tissues a reality and developing tissue-re-

lated technologies. The award will be combined with over $214 million contributed by a consortium made up of industry, state and local governments, universities, community colleges, and nonprofit organizations located across the country to create the Advanced Tissue Biofabrication (ATB) Manufacturing USA Institute. ARMI is located in the Manchester Millyard, a complex of buildings once home to a large textiles maker.

CREATING AN ENTREPRENEURIAL ECOSYSTEM

New Hampshire is home to 270 life sciences companies. Many of its newest companies are spinoffs from academia. Dartmouth College, the only Ivy League university in the state, with its Geisel School of Medicine and Thayer School of Engineering, is located in Hanover. The area is known as the Upper Valley (named for a portion of the Connecticut River watershed that also includes part of Vermont) and, not surprisingly, is home to a growing regional center for biotech, in general, and biopharma, in particular.

"The idea is, if you invent something here, we allow you to start a company in exchange for 4 percent founding ownership."

TILLMAN GERNGROSS, PH.D.
Dartmouth College

Much of the Upper Valley's biopharma industry has grown organically thanks to the presence of talented academic researchers, like Tillman Gerngross, Ph.D., a professor of engineering who has started five life sciences companies. In recent years, Gerngross has been among the Dartmouth leadership working to intentionally grow the Upper Valley's entrepreneurial ecosystem. The goal is to attract and encourage entrepreneurial researchers with its innovative approach to IP, support for founders of startups through the Dartmouth Entrepreneurial Network (DEN), and by providing workspaces both on campus at the DEN Innovation Center and at the Dartmouth Regional Technology Center (DRTC) in nearby Lebanon. DEN was created in 2001 and provides faculty with entrepreneurial education, networking opportunities, matchmaking, and early-stage funding. The DRTC, which opened its doors in 2006, allows spinoff companies to rent space until they are ready to graduate and move out on their own. "We have intentionally evolved DEN as a key startup support mechanism in the institution to help faculty members translate research and ideas into new ventures," says Jamie Coughlin, the college's director of entrepreneurship. "We are creating a pipeline of early-stage startups, positioning Dartmouth to realize its goal of creating a vibrant entrepreneurial ecosystem."

Dartmouth's Gerngross exemplifies the local entrepreneurial spirit of the Upper Valley. His first company, GlycoFi, developed a yeast-based technology used to manufacture drugs. It sold to Merck in 2006 for $400 million. Merck stayed in the Upper Valley for 10 years, moving GlycoFi employees to Boston last year. Gerngross is the founding CEO of Lebanon-based Adimab, a company that focuses on antibody discovery and optimization. Started in 2007, the company is now worth $2 billion and employs just under 100 people. He also started a company that focuses on the purification of biologic drugs and is based at the DRTC. (He also started two other life sciences companies located outside of New Hampshire.) He credits his early success to support from his dean, as well as a network of venture capitalists with Dartmouth ties. "Dartmouth is well-represented in the VC community," says Gerngross. "If you have good ideas, you can get in front of the most experienced and successful investors in the country."

In recent years, Gerngross has worked to make Dartmouth's already supportive entrepreneurial environment even more so. As associate provost of Dartmouth's Office of Entrepreneurship and Technology Transfer from 2013 to 2016, he oversaw the implementation of a new IP policy that he hopes will attract like-minded entrepreneurial faculty and foster innovation. "Our intent is to make it as easy as possible for inventors to take IP and start companies." Most universities keep a tight rein on IP rights, often ending up haggling over licensing terms. "I didn't want us to be on the other side of our faculty. The idea is, if you invent something here, we allow you to start a company in exchange for 4 percent founding ownership." Gerngross points out that the policy has been in place for only 18 months and that time will tell if it will be responsible for growth in the local tech industry. He hopes other universities will follow Dartmouth's lead in taking the adversarial dynamic out of academic entrepreneurship.

Trip Davis, chairman of the DRTC and entrepreneur-in-residence at the DEN Innovation Center, hopes the flow of companies coming out of the pipeline the college has built increases in the coming years. "We are not going to be the next Cambridge, but we will allow companies to grow and become world experts in their respective niches. It's a mistake to try to be the next Silicon Valley. Instead, it's better to enable organizations to build on their expertise, build world-class technology, and make world-class products." L

Alternatives To Funding Lower-Priority Trials

SUZANNE ELVIDGE Contributing Writer @SuzanneWriter

While some pharma companies struggle to backfill their pipelines, others find the opposite, that they have more development opportunities than they can pursue. While this may seem to be a nice problem to have — the luxury to be able to choose the very best of the very best — it also means that otherwise good drug candidates may be pushed down the list of priorities.

THE CHALLENGE OF TOO MUCH CHOICE

Agreements with academic institutions or smaller pharma companies often are the cause of companies having too many development candidates to choose from. This scenario also can be the result of a merger or acquisition, where the two companies have candidates that effectively duplicate each other or are not aligned with the newly consolidated company's core area. Other reasons for drugs not being developed include a company or competitor shifting focus but not necessarily wanting to divest the drug, or if a project with a shorter timeline or a higher potential revenue stream takes priority, thus shifting planned trials.

The current business climate is squeezed for resources and demands a good return on investment. Because of this, companies, particularly those with shareholders, feel beholden to select the candidates that have the best chance of getting to the market and making a profit. This may be by selling large volumes or by targeting a smaller market that can bear a higher price.

"Some companies may not have the resources to develop all the drugs in their pipeline or may have the resources but feel that the drugs are not as promising as they would like," said Ben van der Schaaf, principal at Arthur D. Little, an international management consulting firm. "Because of their focus on shareholders, Big Pharma companies are often after blockbusters, not drugs that make just a few hundred million."

This leaves preclinical or even clinical stage drugs whose development may be terminated or forgotten for so long at the back of the (virtual) cupboard or fridge that their patent life becomes too short for economic development.

Moving drugs around in the pipeline may seem simply like the reprioritization of products seen in any industry, but van der Schaaf sees it as an issue with greater ramifications than simply business: "It means that promising drugs don't get developed, meaning a loss of value and investment within a company and a group of patients that doesn't get access to a potential treatment. The impact, of course, would be greater if it was an orphan disease."

BENEFITS OF NEW PARTNERSHIP MODEL FOR DEVELOPING LOWER-PRIORITY PROJECTS

- Lower development costs
- Funding without dilution or loss of control for the pharma company
- Less risk
- Meeting social responsibilities (e.g., for orphan diseases)

FINDING AND FUNDING A SOLUTION

Partnership has long been a way of spreading the costs of drug development, and models vary, including where equal partners share the work and the expense, or where one company funds research carried out by another. Partnerships can involve equity investment, leading to dilution, as well as loss of control over the product or the company's development, and may not be the best option for a noncore project.

A team at Arthur D. Little has developed a new partnership model that could provide a route to developing these lower-priority projects at lower cost to the company by bringing in outside parties. As well as the company that owns the asset, the model would include one or more CROs to carry out the development and investors to fund the project. The investors could be traditional venture capital groups or nonprofit organizations that have specific objectives in healthcare.

> *"[Traditional investors] still want to see a sound return, and are unlikely to commit until they can see the portfolio."*
>
> **BEN VAN DER SCHAAF**
> Principal, Arthur D. Little

So, what's in it for the partners? This approach provides an alternative route to funding without dilution or loss of control for the pharmaceutical company. It also allows the pharma company to pursue lower-priority areas at less risk. If addressing an orphan disease or meeting an unmet need in developing countries, this approach also could be seen as meeting social responsibilities.

"We are talking to pharmaceutical companies, and at least one is actively exploring the idea. The approach is attractive to them as it helps them to explore part of their portfolio that wouldn't otherwise be developed, and could add value," said van der Schaaf.

CROs could view the approach simply as a long-term contract that uses their standard processes and in-house knowledge and gives them access to a stable revenue stream, or as a way to gain experience in new therapeutic areas or in drug development. Some CROs have investment arms, so they could come on board as an investor as well. For the nonprofit investors, the model would help them to support development of drugs in areas that might otherwise be seen as unattractive by pharmaceutical companies.

"For nonprofit organizations such as the Gates Foundation, working with a pharmaceutical company in drug development can fit into their mission statement, for example by creating a therapeutic for a rare disease, or a lower-cost drug for a disease like malaria in a low-income country," said van der Schaaf.

The Cystic Fibrosis Foundation (CFF) has taken a step towards this approach already, through its venture philanthropy model. The foundation provides early-stage funding for pharma and biotech companies that are working on drugs in cystic fibrosis, making its first large investment in 2000, when it provided Aurora Biosciences (now Vertex Pharmaceuticals) with $40 million to develop drugs targeting the core genetic defect in cystic fibrosis. This investment provided a solid return on investment when CFF sold its royalty rights for the Vertex cystic fibrosis treatments in 2014 for $3.3 billion, which could then be reinvested into research and development.

And finally, the traditional investors would look for a payoff to provide a return on investment, so they may be interested in drugs with a more mainstream profile.

"We have also found that there are traditional investors who like the idea — if the portfolio is right and the returns are attractive, then they want to invest. However, they will still want to see a sound return, and are unlikely to commit until they can see the portfolio," said van der Schaaf.

BUILDING THE MODEL

The first step in the process would, as with any agreement, be a portfolio analysis and due diligence. While this business model isn't the same as a licensing agreement, there also still needs to be a clear agreement put in place at the beginning of the process, addressing intellectual property, patents and know-how, and what happens with any products developed as part of the deal. This will vary between the three types of investors, and even from deal to deal.

The future of the model could be creating a vehicle that includes more than one pharma or biotech company. This would need to balance collaboration and competition, and would increase the pressure on information sharing.

"We see lots of benefits to this approach, but are aware that it also carries risks and challenges. But we believe that it has potential to work," concluded van der Schaaf. L

Rising Out Of Takeda's Reorganization: New Materials & Innovation

LOUIS GARGUILO Chief Editor, Outsourced Pharma @Louis_Garguilo

As the taxi makes its way through the highway traffic to Shin-Osaka Station and the bullet train I'll catch to head east to Tokyo, I know instinctively to look out the right-side window. Yes, it's still there: the nostalgic off-ramp leading directly to Takeda's former main manufacturing complex.

The company moved much of its operations from Osaka to the Tokyo area — and indeed started spreading internationally — years ago. In fact, no "Japan Pharma" has ever been more on the move than the now global Takeda.

Coincidentally, a few weeks before my visit to Japan, I received a call to my New York office from Vincent Ling of Takeda. Readers of *Life Science Leader* may recall that Ling (based at Takeda Boston) and I previously collaborated on an article regarding nanomedicine. When I asked Ling what came out of the reorganization recently put in place by Andrew Plump, Takeda's new chief medical and scientific officer (CMSO), he replied: "New materials and innovation!" and let out his signature laugh. "I knew you'd be interested," he added.

He was mirthfully correct. And readers also will be interested in learning of this practical application of Takeda's new strategic vision.

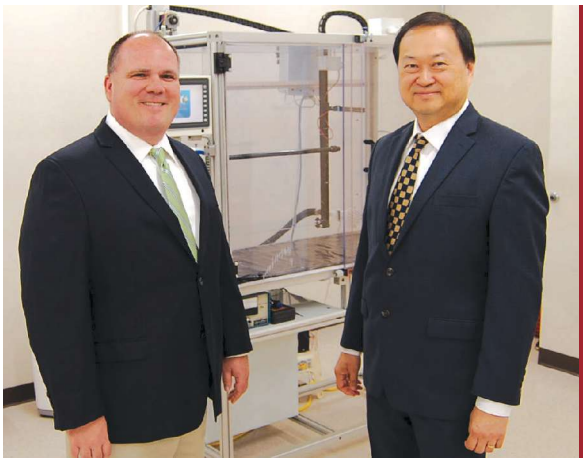
THE MATERIALS AND INNOVATION GROUP

As part of Takeda's broad rethinking vis-à-vis R&D, detailed recently in a separate *Life Science Leader* interview with Plump (by our executive editor, Wayne Koberstein), Ling was tasked with forming a new unit and then appointed senior director in Takeda's newly created Materials and Innovation Group. "Our founding strategy recognizes you don't have time to invest in basic research and wait 10 years," says Ling. "You have to go find individuals and companies doing exciting research, engage them, and progress those new technologies through collaborations and funding."

And Ling has long held his own thoughts on bringing new and more efficient therapies to patients: "Frankly, I'm not convinced the future of medicine can be based only on drug discovery. We have to be much more nuanced. There will be new modalities, such as medical therapy based on biomaterials. It'll be great if we have drugs present in those materials, but in many cases that may not be necessary. It's the therapy itself that counts."

Ling's group resides within the Pharmaceutical Sciences Department, under the direct umbrella of Formulations Development, which houses professionals who create injectables, innovate formulations, and think through delivery of the drug-molecule candidates that come out of screening. "These scientists are less tied into specific disease target areas and more into the technologies that create better therapeutics. It's the best division of Takeda to establish a bio and nanomaterials initiative," says Ling.

Ling also has believed for some time that those inhabiting the drug discovery arena are "so focused on equating therapy with a trendy molecule that they forget biology reaches well beyond that single focus." He's looking for higher acknowledgment that interactions between drug molecules are complex, and drugs widely affect physiology throughout the body. "If, on the other hand," says Ling, "you consider implanted biomaterials



"Our founding strategy recognizes you don't have time to invest in basic research and wait 10 years."

VINCENT LING
Senior Director, Takeda Materials and Innovation
Pictured with Matthew Phaneuf (left), President & CTO, BioSurfaces, Inc.

can be localized to one area and have new and unique physiological interactions, that creates new research space for therapeutics. There's a whole dimension that most early-stage drug discovery scientists haven't fully opened up to."

One reason for this relatively myopic drug-first approach in pharma is that biomaterials are generally considered as medical devices. Unfortunately, Ling also sees a challenge on the medical device end of the spectrum. "The funny thing is, inversely, the people in the medical device world don't want to think of their materials as having drug-like properties, since the regulatory approval pathway for drugs is more arduous than for devices. That opens a whole can of worms for them; mostly they aren't ready to deal with it." And thus Ling — enabled by the open thinking of Takeda senior leadership — is setting out on a middle path. "We're entering our first days to proceed independently from a therapeutic, molecule-first approach, to a pure materials-based approach for medical therapies. To the best of my knowledge, no other pharmaceutical company is doing exactly what we are doing."

STARTING POINTS AND "S" CURVES

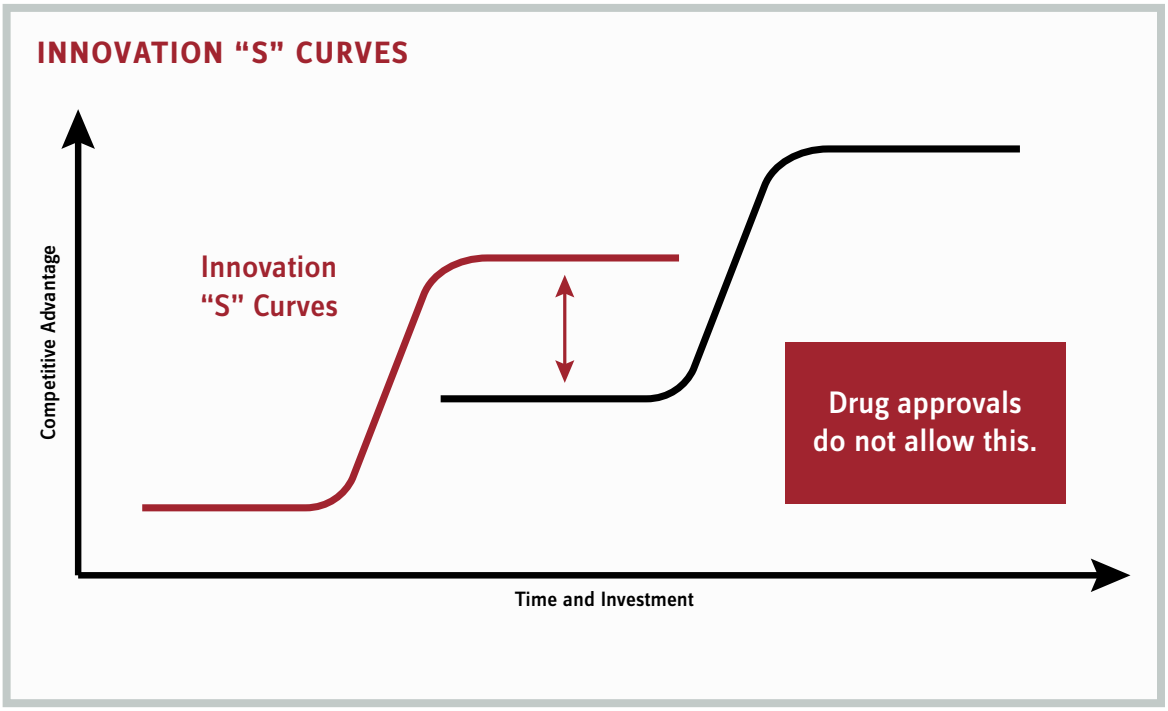
Ling, who has 20+ years of biologics drug discovery experience, has always been an ardent student of innovation. He uses EROOM's law (Moore's law of productivity in reverse) to graph how the cost of drug discovery has become prohibitively expensive at the same time that results — new drug approvals — have consistently diminished. Ling also employs the concept created by Clayton Christensen, made famous in his book *The Innovator's Dilemma*. Christensen created a standard "S" graph plotting the life cycle of innovation from the aspects of competitive advantage and time and investment.

This innovation model starts out with little measurable activity or results (the bottom of the red "S" in the graph on page 40). At a certain point, though, research efforts break through to a scientific or technological advance, which eventually plateaus again, as technology saturates markets. PCs and laptops, whose basic function was new and groundbreaking 20 years ago, experienced this tremendous growth trend and then became a standardized commodity. These machines certainly haven't gone away, but their innovative impact diminished, signaling the time for another breakthrough innovation, such as cell phones (represented by the second, black "S" in our graph on page 40).

Unfortunately — and a major detriment to our current drug discovery productivity — new innovation (the black "S") typically starts from what might initially be considered an inferior point, or for niche purposes, and not at the crest of the first "S." Cell phones were initially considered rather one-dimensional, but transformed into smartphones and other mobile devices, severely impacting the personal computing industry (not to mention the music, photography and other industries).

"This is the way everybody understands innovation in their gut," Ling says. "Except this model does not apply to the pharma industry. It has to abide by the rules of the FDA." What he means is drug developers cannot bring a therapy to market by starting out *worse* than competing standards of care; it'll fail clinical trials. Because of the travails of trial methodology, companies attempt to "saturate their original innovation with more money and effort, for example on biosimilars and add-on combo therapies, but impacts in technological improvement are diminished." An example of pharma's effort to avoid this battle of diminishing returns on saturated technology is the embrace of rare diseases and unmet medical needs, where there may be no preexisting "S" curve to displace.

Circling back to Ling's earlier point, another challenge here is in the way most pharma companies are wound tightly around core therapeutic areas. Even



brilliant ideas and new relationships from outside the company must initially fit within these therapeutic groups. Pharma devises and extolls "open external research centers" and the like, but these, too, ultimately remain therapeutic-area determinate. Inventions that are slightly outside the therapeutic target area are often ignored. Therefore, Ling believes a solution lies in new thinking, such as focusing on medical treatments somewhere between drugs and material science. "That's how I'm thinking of our new Materials and Innovation Group," he says. "I'm proposing a middle ground for innovation that's more open, but can still work within the regulatory and organizational constraints of the pharma industry."

IT MIGHT NOT EVEN BE A DRUG

Still, Ling says his thinking can work within the company's larger therapeutic framework. While his newly formed group aims to make medical therapies that don't have to be drug-related, he can still be guided by Takeda's core therapeutic areas — central nervous system (CNS), gastroenterology, oncology, and vaccines. "We are looking at materials innovation — new bio or nano materials and new systems of delivery — that can be applied to our core," he says.

This doesn't keep Ling from thinking his more expansive thoughts. He references a discussion he and I had when preparing our first article on nanoparticles ("Takeda CEO Mandate Sets Off A Nano Reaction"; *Life Science Leader,* April 2016). "When you mentioned the idea that nanotechnology can be the actual therapy, I could not have agreed more, and in fact have been working on that thesis," he tells me. [Editor's Note: Attribution for my initial understanding on this subject goes to Laurent Levy, CEO of Paris-based Nanobiotix. See "Can Nano Bring Us Back From Personalized To Mass Medicine?" *Life Science Leader,* August 2015]. That notwithstanding, Ling is clear there's no predetermined path for the Materials and Innovation Group, which is starting out with a dozen or so group members, "some in the lab and others scouring near and far for external research related to material-type innovations." The scavengers will find inventors, and the whole team will try to determine what might be "the killer application for their invention to treat the diseases we're focused on."

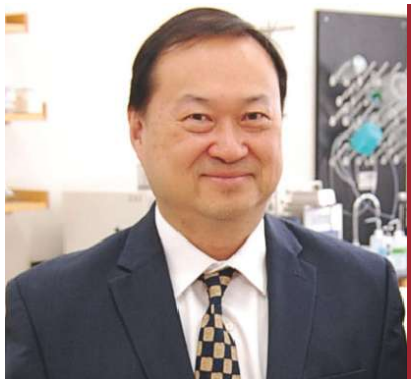
Ling's prerequisites to garner interest and potential investment are twofold: a seed-stage entity, and a strict three-year research window. He's looking primarily for implantables and localized therapies. "I try to avoid injecting and having systemic exposure," he says. "I like therapies locally applied to a certain lesion in the body." In fact, as we were preparing this article, Ling and Takeda announced they'd found their first relationship, with a company called BioSurfaces, Inc., of Ashland, MA. I then had the opportunity to bring Matthew Phaneuf, president and CTO, into our discussion. What became apparent was that this first collaboration both exemplifies the kind of company and technology Ling is pursuing, and as

importantly, how his approach leads to opportunity in the first place.

ELECTROSPINNING AND BIOFACTORIES

Let's start with the approach: Ling himself decides to attend a local (Boston) investor-pitch conference to begin evaluating different technologies. He sits in on a company presenting technology related to hemodialysis access applications. "I know Takeda won't be interested in investing in this area; it was clearly out of focus," Ling says, "but they are mentioning special properties of a new nanostructure material. I quickly get interested."

Phaneuf, also seated in the audience, recalls: "Vincent asks the only question there was time for. It was focused on the healing response of our materials." Phaneuf's answer to that question starts up a months-long dialogue during which he says he studies "how to marry Vincent's vision to the greatest use of our technology." Takeda gives BioSurfaces some early feasibility studies to ensure "what they suggested really happens." "It does," says Ling. Now with an executed contract, Phaneuf is excited to talk about some of the technology he may get to apply to projects with Takeda, but also some thoughts for the future, including applications for nanomaterials created through a process called electrospinning.



> *"My pitch when we were forming our group was, 'Hey, we're a medical technology group. We think differently. Let's consider going to nano and other materials, someday even to the point of having the materials be at the core of the medicine."*
>
> **VINCENT LING**
> Senior Director, Takeda Materials and Innovation

Electrospinning is a technique by which BioSurfaces puts polymers and other materials into a solution state, and then applies a voltage as the solution is drawn out of a syringe. "We can create materials that possess excellent healing properties, and can be engineered to deliver drugs, or used to house specific therapeutic cells," explains Phaneuf. The typical fiber diameter comprising a medical device is approximately 30 microns; BioSurfaces' fibers can have diameters down to 0.5 microns, or 500 nanometers. "Put in perspective, that's 120 times smaller than the average human hair, or about 1/20th the size of a human cell. This subcellular-fiber size promotes tissue healing when implanted."

The technology can be used to deliver single or multiple drugs locally to a disease site, without requiring the fiber to break down, unlike drug-eluting stents that require the polymer to break down to release a drug. Phaneuf says a single-step manufacturing process offers the ability to load the drug throughout each fiber. "Each fiber serves as a reservoir, providing a significant amount of surface area to deliver the drug," he explains. "This allows the drug to be released without affecting the overall healing properties of the material."

But there's more, and someday it could prove herculean for our industry. Phaneuf has demonstrated that these electrospun nanofibers can encapsulate cells and create a "biofactory," which is placed at a specific location in the body. "We are talking about an implantable device with cells that continuously secrete additional proteins with therapeutic benefit," he explains. "Basically, we're now using the body's own mechanism — its own nutrients — to feed the cells, and have those cells confer a local treatment over an extended period of time. The therapeutic can be released across the wall of the material and delivered to the patient, right at the site of the disease. It really is, in this regard, a working biofactory in the body."

Of course still out there is our earlier-discussed — and perhaps most elegant — concept of all, one that would certainly delight Ling and be transformative to our industry: Have the nanomaterials themselves provide the medicinal effects via their nanostructuring. In other words, no drug need apply. And while all of this is still to be thought out and tested, it's clear Takeda's new Materials and Innovation Group is off to an exciting start with BioSurfaces. Ling concludes: "My pitch when we were forming our group was, 'Hey, we're a medical technology group. We think differently. Let's consider going to nano and other materials, someday even to the point of having the materials be at the core of the medicine.'" He adds with his signature laugh: "Let's rock the world."

Government Funding And Technology: The Right Ticket For Small Pharma

ED MISETA Chief Editor, Clinical Leader @EdClinical

Small pharmaceutical and biotech companies often face difficulties raising money to fund their research, especially when they get to the point where they need to undergo lengthy and expensive Phase 3 trials. This is especially true when the company does not have a commercial product bringing revenue in the door. When costs begin to increase and cash is hard to come by, government grants and contracts can be one way to help fund research.

Soligenix is a late-stage biopharmaceutical company focused on rare diseases. The company has two main areas of focus. The first is a therapeutics segment dedicated to developing products for patients with orphan diseases and areas of unmet medical need. One product is in Phase 3 testing with another two expected to enter Phase 3 trials in 2017.

But the company also has a vaccines/biodefense segment that develops vaccines and therapeutics for military and civilian applications, primarily the areas of ricin exposure, gastrointestinal acute radiation syndrome, and emerging infectious diseases, such as melioidosis. "Our leading candidate in the vaccine program is RiVax, which has received orphan-drug designation from the FDA," says Christopher Schaber, president and CEO of the company.

ASSISTANCE WITH RESEARCH FUNDING

Taking that many products through the development process can be expensive. Fortunately, research on the ricin vaccine has been funded by the NIH. The vaccine has been tested in a nonhuman primate (NHP) study and has demonstrated 100 percent protection or efficacy from ricin toxin. It was also used in two Phase 1 studies in healthy human volunteers, which demonstrated the safety of the antigen. "We think the funding will get us pretty close to a biologics licensing application (BLA) or new drug application (NDA) equivalent, by the end of the contract," says Schaber.

> *"We think the funding will get us pretty close to a biologics licensing application (BLA) or new drug application (NDA) equivalent."*
>
> **CHRISTOPHER SCHABER**
> President & CEO, Soligenix

You might think funding of this type would come from the DOD. But Schaber notes when it comes to development research for Soligenix, funding has come primarily through NIH and BARDA (Biomedical Advanced Research and Development Authority), which have a focus in biodefense. BARDA also provided funding for the Soligenix OrbeShield program, a therapeutic for GI Acute Radiation Syndrome, and Soligenix will be pursuing both the NIH and BARDA for additional funding.

Sources of funding for development of both medical countermeasures in biodefense and for other rare, unmet medical needs can come from a variety of

2017 HBA Annual Conference

6-8 November | Philadelphia

More than 1,000 healthcare leaders are expected for

- pre-conference seminars
- main-stage (plenary) presentations
- more than 20 interactive workshops
- network-building and social events
- exhibit hall
- Reading Terminal Market reception
- "Tri" movie screening

Keynote speakers

Vernice "FlyGirl" Armour
America's first African American combat pilot

Angela Duckworth
psychologist, professor of psychology at the University of Pennsylvania, co-founder of the Character Lab and author of *Grit: The Power of Passion and Perseverance*, a *New York Times* bestseller

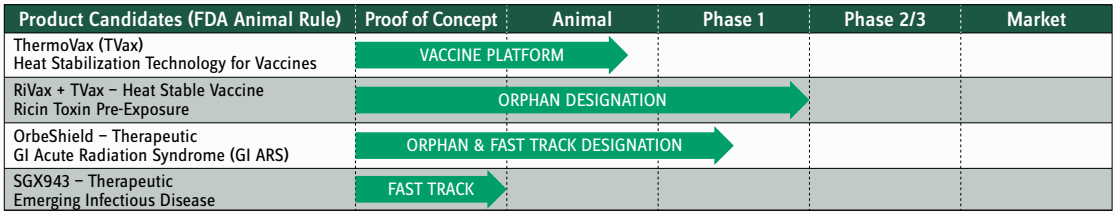
HBA
Healthcare Businesswomen's Association
Connect Share Grow

Register by 21 September for the best rates

HBAnet.org/2017-annual-conference | #HBAimpact

SOLIGENIX VACCINES/BIODEFENSE* PIPELINE

Denotes funding in whole or in part by NIH, BARDA, and/or FDA



* Potential value drivers dependent on continued government funding and/or other funding sources.

sources. For instance, various divisions of the NIH are focused on different therapeutic areas, including significant funding for biodefense. BARDA is primarily focused on the development of medical countermeasures where the commercial market may not otherwise support the development of the required drugs and devices. Soligenix has been successful with a number of grant and contract applications to both NIAID (National Institute of Allergy and Infectious Diseases) and BARDA.

"As we get closer to potential Emergency Use Authorization, licensing, and ultimately procurement, working closely with government agencies such as the DOD and BARDA is also feasible," says Schaber. "There is also a possibility we could work with government agencies outside the U.S."

SPECIALTY PRODUCTS REQUIRE SPECIALTY CLINICAL EXPERTISE

Biodefense products, including vaccines and therapeutics, are generally developed via the FDA Animal Rule where typical clinical efficacy studies would not be ethical. Clinical trials for these products obviously do not expose humans to dangerous toxins. Therefore, the efficacy studies that would normally take place in humans must instead take place in animals. According to Schaber, those studies often may include two animal species, for example a mouse and an NHP. Ultimately the pivotal study will typically take place in an NHP.

"The antibodies generated from the vaccination in the animals would be correlated with antibodies generated by a healthy human simply being treated with the vaccine," says Schaber. "Connect the dots between the human and the animal and we are able to show the results are comparable."

As Soligenix does not have the capabilities to perform animal testing, it uses a preclinical CRO specializing in biodefense to conduct the research. The CRO is approved and cleared by the government to conduct these tests and to handle toxins such as anthrax and ricin. Soligenix must provide the development oversight and knowledge of its vaccine, which also includes vaccine manufacture and leading program activities and interactions with the government agencies.

VACCINES FUND THERAPIES

When funding comes from government contracts, sponsor companies, among other things, need to present a plan of action. Soligenix will create a development plan and corresponding budget detailing what it will accomplish over the term of the contract. That plan and budget are submitted for approval to the NIH or BARDA. Generally, the dollar amount is proposed by Soligenix and negotiated with the respective government agency. For the ricin vaccine RiVax program, the NIH contract could amount to as much as $24.7 million, with the actual figure contingent on development milestones being met. "That not only covers the activities of moving the program through development, it supports all of the indirect costs associated with the program, for example, the facility overhead fees, salary costs, and the management fee for the contract," states Schaber. "The latter, which is also negotiated with the contracting government agency, can potentially range from 6 to 8 percent of the overall contract and is money the company can put into its biodefense program(s) or redirect to the areas where it is most needed."

Oftentimes, Soligenix will direct a percentage of that money into the therapeutic side of the pipeline. Soligenix is a small business entity of approximately 20 employees, so those management fees have the potential to cover a good portion of the company's related expenses.

Small companies working on treatments for cancer or other diseases will often struggle to maintain cash flow for projects, especially when there are no commercial products generating revenue. This is where the government support can be a big help. "In drug development, it seems you can never have enough money. Everything you do is very expensive, especially on the clinical side. But having some level of government support helps us manage that cash burn, and it has afforded us the opportunity to build out a robust product pipeline," Schaber concludes.

How The FDA Views Natural Language Processing

GAIL DUTTON Contributing Writer @GailLDutton

Natural language processing (NLP) can be a useful way to extract meaningful information from unstructured data, such as text and tables from electronic health records (EHRs), journals, and social media, but it isn't ready for full-scale use, according to speakers at the FDA's June workshop Use of Natural Language Processing to Extract Information from Clinical Text.

"The FDA's goal is to personalize NLP capabilities to make our medical officers more effective when reviewing adverse events," Mark Walderhaug, Ph.D., CBER (Center for Biologics Evaluation and Research), said. Workshop speakers suggested NLP may be used to support evidence generation and to improve the scientific validity of efficacy, safety, and post-marketing submissions. It also may find applications in IND (investigational new drug) safety reports, NDA (new drug application) and BLA (biologic license application) submissions, labels, adverse event reports, pharmacoepidemiological studies, and social media and internet queries.

NLP-derived clinical evidence hasn't yet been included in regulatory submission documents, however. Doing so today would be disruptive to assumptions of data integrity and could jeopardize acceptances, speakers cautioned. To minimize that risk (if used with regulatory submissions), they recommend ensuring the NLP extraction process is transparent and leaves an audit trail.

NLP'S VALUE FOR PHARMA

For drug developers, mining comments from text using NLP offers three main benefits: filling in knowledge gaps left by coded data, extracting adverse events information, and improving sample sets by accessing much more data.

Many details of a patient's reaction to a drug or events affecting outcome — like major bleeding or smoking — often aren't coded. Yet, they are important in understanding adverse events. By mining EHRs' text, NLP can fill many of those gaps.

In regard to heart disease, for example, Russ Altman, M.D., Ph.D., Stanford University, cited a study in which only 46 percent of the 101 charts contained structured wound information. NLP mined the unstructured notes, extracting terms like "venous stasis and RLE ulcers" that indicated wounds.

Nigam Shah, Ph.D., associate professor of medicine and of biomedical data science at Stanford University, found similar inadequacies with the coding for patients treated for prostate surgery. "The coding for urinary incontinence was practically nonexistent, but some of the records mentioned urinary incontinence in the text. By mining the notes, there is about a 100-fold increase in the things you find, and you can get negative information — such as 'no urinary incontinence' — which you can't get from the codes."

Shah also found NLP helpful in searching for events to aid in phenotyping for Alzheimer's, Parkinson's, and multiple sclerosis.

HOW NLP IS BEING USED NOW

NLP has been used by companies such as Shire and Lilly for drug discovery and clinical trials as well as European regulators to compare codes in submission and quality assurance documents.

Lixia Yao, Ph.D., assistant professor at the Mayo Clinic, and colleagues mined social media and EHRs for off-label drug uses, identifying several opportunities for drug repurposing. The search also showed that, among social media, "YouTube and Twitter had

OutsourcedPharma
CONFERENCE AND EXHIBITION

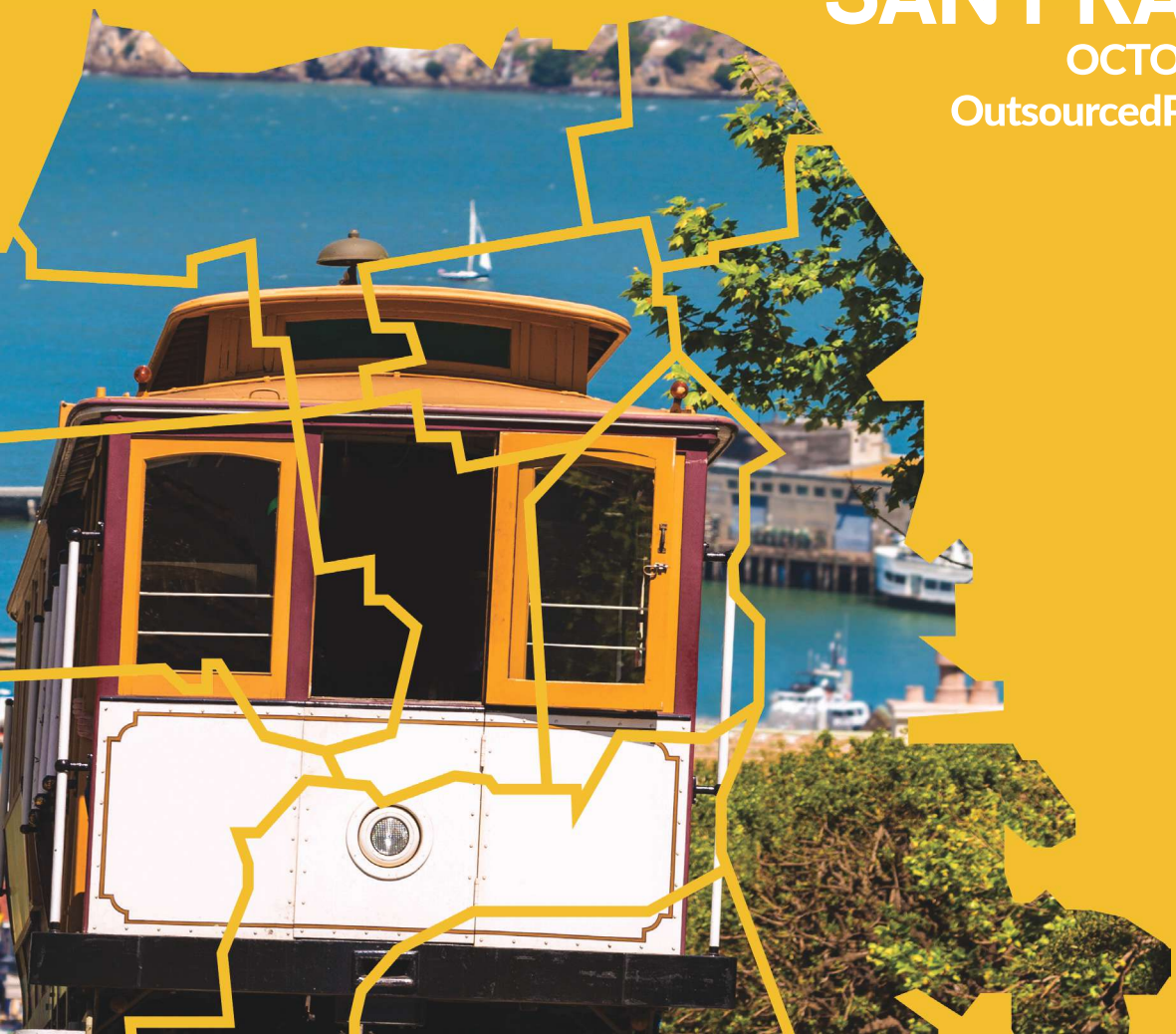
TRANSFERENCE IN DRUG DEVELOPMENT AND MANUFACTURING OUTSOURCING

Produced by *Life Science Leader* magazine and OutsourcedPharma.com, Outsourced Pharma Conference & Exhibition is a vibrant forum for thought-leadership and the application of best practices for professionals engaged in outsourcing drug development and manufacturing.

SAN FRANCISCO

OCTOBER 17 - 18, 2017

OutsourcedPharmaEvents.com



larger followings, but WebMD and PatientsLikeMe had better-quality information," Yao said. "In general, people post if they are disappointed or angry. Therefore, individual data sources have inherent biases and may only provide one piece of the puzzle."

At the FDA, CDER is piloting a study with Veterans Affairs to determine how patient behaviors affect outcomes among smokers with lung cancer. CDER is especially interested in learning whether NLP can identify variables missing from Big Data or spot biases that may color the findings.

Another FDA project uses NLP to mine the FDA Adverse Event Reporting System (FAERS). This approach has identified causal relationships between products and adverse events and helps reviewers more accurately summarize the cases.

The FDA also is mining ARIA, the FDA's active risk identification and analysis system, to identify signals of serious, unexpected risk related to certain medications. "The algorithms lack the judgment of human experts and need to improve," cautions Robert Ball, M.D., deputy director, office of surveillance and epidemiology, CDER. "Nonetheless, we can use NLP for a deeper look at what's happening in a case."

HIGH ACCURACY RATES

Accuracy rates for NLP have ranged as high as the upper 90s, but a literature review indicates ranges of about 85 to 95 percent are more typical. That's accurate enough to use NLP to mine data for probable causes of disease, refine case definitions, find adverse events, support decisions, and identify changes in patients' conditions.

"Linking data sources improves overall performance," Altman said. Speakers also advised using multiple versions of search terms — weight, weighing, wt., etc. — and allowing for typographical errors. Additional steps include allowing the system to infer information — that simvastatin is a statin or that certain weights indicate obesity, for example — and differentiating between positive and negative mentions (like "I have cancer" versus "I don't have cancer") and to avoid confusing family histories with present conditions.

ADAPTING NLP FOR MULTISITE USE

Today NLP is most effective within single sites. Multisite use for product and safety surveillance, where many outcomes are captured only in unstructured narratives, is feasible but not easy.

One of the greatest challenges in adapting NLP to multisite applications is assembling a complete and representative clinical corpora because different sites, even within the same healthcare system, have their own cultures and customs that affect information. "Applying NLP in a multisite setting requires forethought and attention to detail because of idiosyncrasies in language usage, document structure, and content," emphasized David Carrell, Ph.D., Kaiser Permanente Washington Health Research Institute.

Additional challenges include incomplete clinical text, differences in interpretation, and the differing needs of researchers and clinicians. For example, reconciling inconsistencies, such as polyps that were recorded before the colonoscopy, can be resolved easily for one patient. Resolving similar issues for hundreds or thousands of patients isn't so simple.

Duplicate records also must be reconciled to ensure the most current EHRs are mined. In a study of 2 million EHRs, many had more than 30 versions and one had 53 different versions.

WHAT'S NEXT FOR NLP?

Refinements in algorithms and search techniques are ongoing. IBM is developing a network of connected knowledge built from de-identified patient records from the Cleveland Clinic. That network was developed by parsing and linking terms from medical concepts, medical dictionaries, and EHRs, as well as identifying the clinicians who authorized treatments and authored the notes, according to Murthy Devarakonda, Ph.D., principal investigator of the Watson Medical Analytics project at IBM Research. The goal is to gain insights into what individual physicians were thinking when ordering tests and making diagnoses.

"At the Mayo Clinic, we're looking at language patterns using regular expressions and extracting sentences using a decision tree," Yao said. The goal is to capture the context of patient- and clinician-generated data.

Several of the presenters expressed interest in deep learning, a form of machine learning. Mimicking the way humans learn, deep-learning algorithms read the same information multiple times, increasing their accuracy with each reading. Devarakonda and his team also are investigating a deep-learning approach that goes beyond extracting keywords to understanding the meaning of passages and sentences, and thereby linking problems to solutions.

KEEP YOUR EYE ON NLP

"Text is only one of many sources of information," Shah stressed. "Rather than focusing on one or the other, look at the synergy between text and coded data. You don't have to get your information using just one technology."

Although NLP isn't expected to be ready for routine use anytime soon, the FDA is seriously evaluating the technology to determine how it can be used by drug developers and the agency to support and evaluate regulatory submissions. L

OutsourcedPharma
CONFERENCE AND EXHIBITION

AN EARLY START ON DRUG DEVELOPMENT AND MANUFACTURING OUTSOURCING

SAN DIEGO

AUGUST 22 - 23, 2017

OutsourcedPharmaEvents.com

SPEAKERS INCLUDE

ABZENA
George Badescu | *VP, Scientific Affairs*

BACKFIELD PLLC
Katlin Backfield | *Attorney at Law & Consultant (former FDA counsel)*

BIOGEN
Dan Gage | *Sr. Sup., Tech Development*

CORTEXYME
David Hennings | *Sr. Dir., Head, CMC*

CRINETICS PHARMACEUTICALS
Ajay Madan | *VP., Development*

ELI LILLY AND COMPANY
Mark Butchko | *Sr. Dir., QA, Product Research & Dev.*

ELUSYS THERAPEUTICS
Dennis Knox | *Sr. Mgr., Quality*

KURA ONCOLOGY, INC.
Xiaohu Deng | *Sr. Dir., Head, CMC*

LATHAM BIOPHARM GROUP
Susan Dexter | *Managing Director*

MABVAX THERAPEUTICS
Paul Maffuid | *EVP, Research and Dev.*

MERCK
Rachael Atlee | *Regional Dir., ExM Sterile Tech-Ops*

NANOMEDICAL DIAGNOSTICS
Francie Barron | *VP, Biology & Reg. Affairs*

NEUROCRINE BIOSCIENCES
Scott Zook | *VP, CMC Dev.*

NOVMETAPHARMA
Peter Lee | *Vice President*

OUTSOURCED PHARMA
Louis Garguilo | *Conference Chair & Chief Editor*

PACIRA PHARMACEUTICALS
Ray Kaczmarek | *VP, Commercial Manufacturing & Supply Operations*

PACKAGING TECHNOLOGIES & INSPECTION
Oliver Stauffer | *CEO*

PFIZER
Firelli Alonso | *Sr. Director, Biotherapeutics & Vaccines Outsourcing*

PFIZER
Bernie Huyghe | *Sr. Director*

PFIZER
Sylvie Sakata | *Sr. Dir., Ext. Research Solutions*

QUALITY CONSULTING ASSOCIATES
Mitchell Rosner | *Principal Consultant*

QURIENT CO. LTD.
Jaeseung Kim | *Sr. Dir., CMC and R&D*

RONDAXE
Brian James | *SVP, Operations*

RX-360 DATA INTEGRITY GROUP
Barbara Unger | *Co-Lead (President, Unger Consulting)*

STA PHARMACEUTICAL, *A WUXI APPTEC COMPANY*
Antonio Garrido-Montalban | *Executive Dir.*

TIOGA RESEARCH, INC.
John Newsam | *CEO*

TOCAGEN, INC.
Doug Jolly | *EVP. Research & Pharma. Dev.*

VERTEX PHARMACEUTICALS
Ben Littler | *Sr. Dir., Process Chemistry*

"Sociopath-Proof" Your Organization:

5 Questions To Ask Today

DR. BRIAN RUSSELL

BRIAN RUSSELL, Ph.D., JD, MBA, solves ethical problems in organizations on TV and radio and in his book *Stop Moaning, Start Owning: How Entitlement Is Ruining America and How Personal Responsibility Can Fix It.*

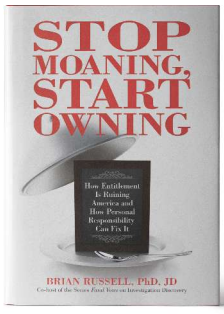
After being expelled from Harvard for a computer hack that altered his transcript, Ajay Thomas changed his name to Mathew Martoma, somehow scored a Wall Street job, and, in 2008, insider-traded shares of two public life science companies to the tune of $275 million. He was caught, convicted, fined $9 million, and sentenced to nine years in prison, yet his parents maintained he was innocent and had been framed.

Sadly, oblivious parents are raising more sociopaths in America today than ever (in one study, approximately a third of high-schoolers admitted to shoplifting in the prior year, yet the vast majority rated themselves high in character). And if they get into your organization, they can do incalculable damage to your reputation and finances. Typical interview questions about ethics won't weed them out, but here are five questions you should consider:

5 QUESTIONS LIFE SCIENCE LEADERS SHOULD ASK THEMSELVES

1. Does everyone in my organization know the values I expect us to embody in everything we do? After physical safety, that's a leader's number-one job, and it's not enough to articulate values — the leader then needs to verify that everyone at every level is getting the message.
2. Am I assessing ethics? While no assessment can guarantee whether someone will do something wrong in the future, you *can* assess past behavior, and you *can* assess how closely applicants' perspectives on ethics match your own; you should be doing both. And if they really matter, you should be assessing ethics not just when hiring but also in subsequent performance evaluations.
3. Does my behavior demonstrate the values I articulate? You should be doing both what you say you'll do and what you expect others to do. If you expect members of your organization not to cross ethical lines, it's best they not walk those lines. To that end, "walking the walk" is more important than "talking the talk"— you should be leading by example and not be walking those lines yourself.
4. Have I made it hard to do the wrong thing? Anyone inclined to cross an ethical line should know you're watching, and if someone's caught crossing a line, you should know that everyone else is watching. If, for instance, they see you give a high-level or high-performing individual a pass, they'll conclude that unethical behavior is acceptable when it's accompanied by position or performance (or worse, they'll conclude that unethical behavior is how to achieve position or performance).
5. Have I made it easy to do the right thing? You should be clear that no one is to be penalized for reporting suspected unethical behavior in good faith and that there's nothing, short of a physical safety hazard, about which you want to be told more urgently (and make it easy to tell you). Lastly, you should be developing people with respect to ethics, coaching them, both on what *not* to do and on what *to* do instead.

While no organization is "sociopath-proof," if you've answered "Yes" to fewer than all five of the above questions, it's likely that more can be done to reduce ethical risk in your organization.

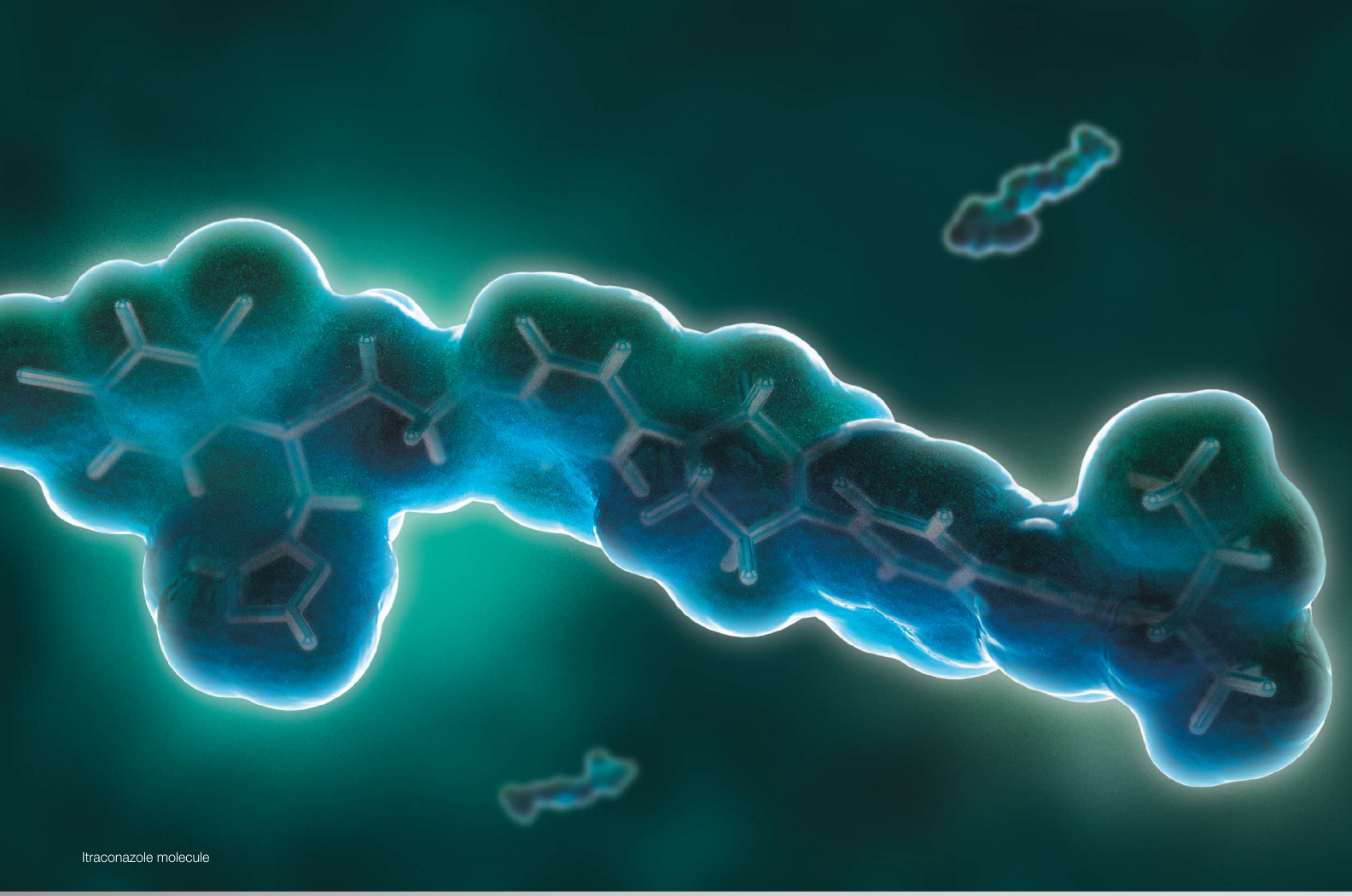


OneSource Laboratory Services: With you every step of the way – to reach *your* best outcomes

In today's complex scientific environments, every lab function has to work in sync toward a common goal. Our OneSource® Laboratory Services team delivers solutions that cover all aspects of your operations and can be customized for the scientific workflows and business outcomes you're striving toward. With proven success at the world's top pharmaceutical and environmentally focused organizations, and managing more than 500,000 assets worldwide, the OneSource team provides a complete services offering with global reach and local support. Together, we're taking business results to the next level.

Learn more at www.perkinelmer.com/onesource

PerkinElmer®
For the Better



Itraconazole molecule

Formula to finished dose. Delivered.

Our clients bring us their one-of-a-kind breakthroughs. Our experience gives them a reliable and efficient journey into viable products. We offer complete drug substance and drug product services for small molecules. Plus, a comprehensive range of dosage forms. Let us apply our expertise to help you overcome your toughest solubility challenges and accelerate your path from concept to proof of concept to commercial launch.

Patheon®

A HEALTHIER WORLD. DELIVERED.