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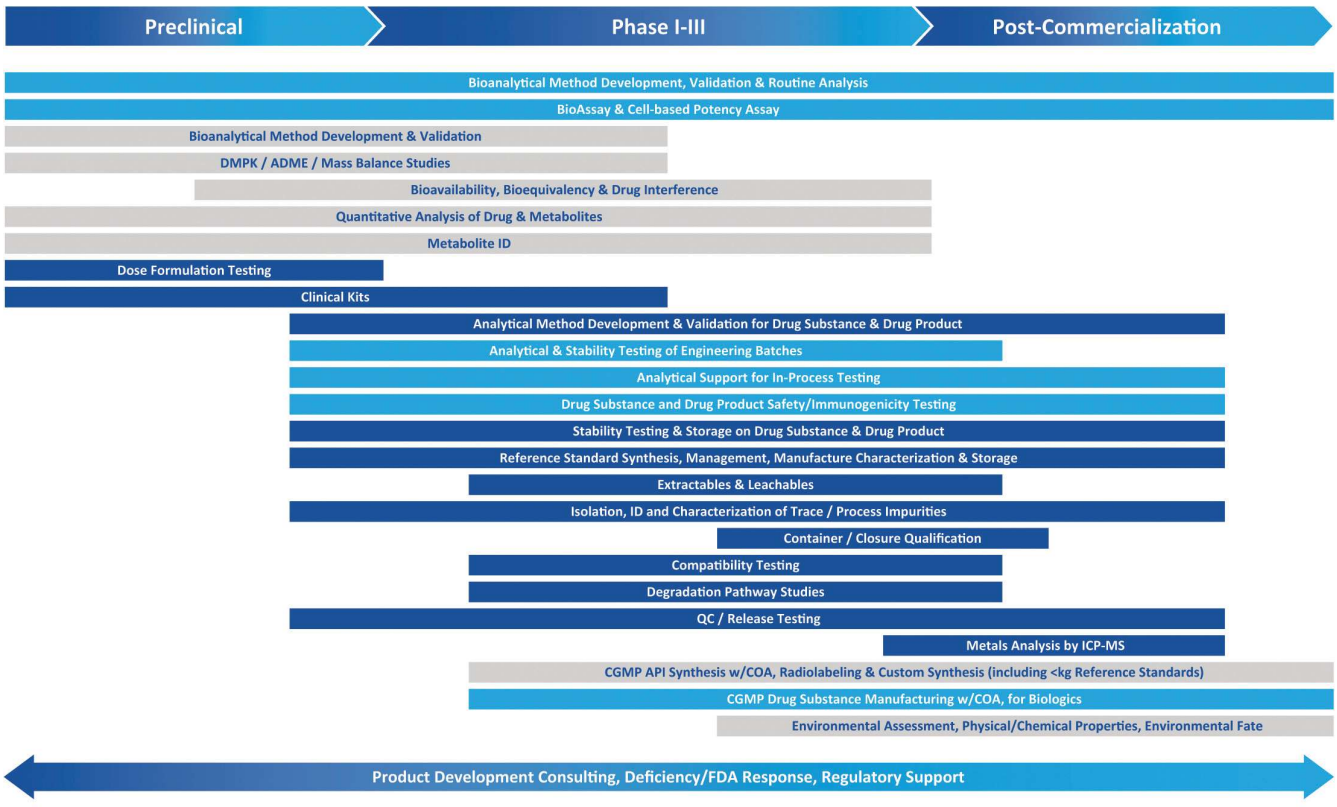

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Pfizer's Path to Patient-centricity

p. 20

"As an organization, we needed to organize our patient-centric thinking, systems, and processes to make it consistently part of what we do every day."

Freda Lewis-Hall, M.D.
Chief Medical Officer at Pfizer

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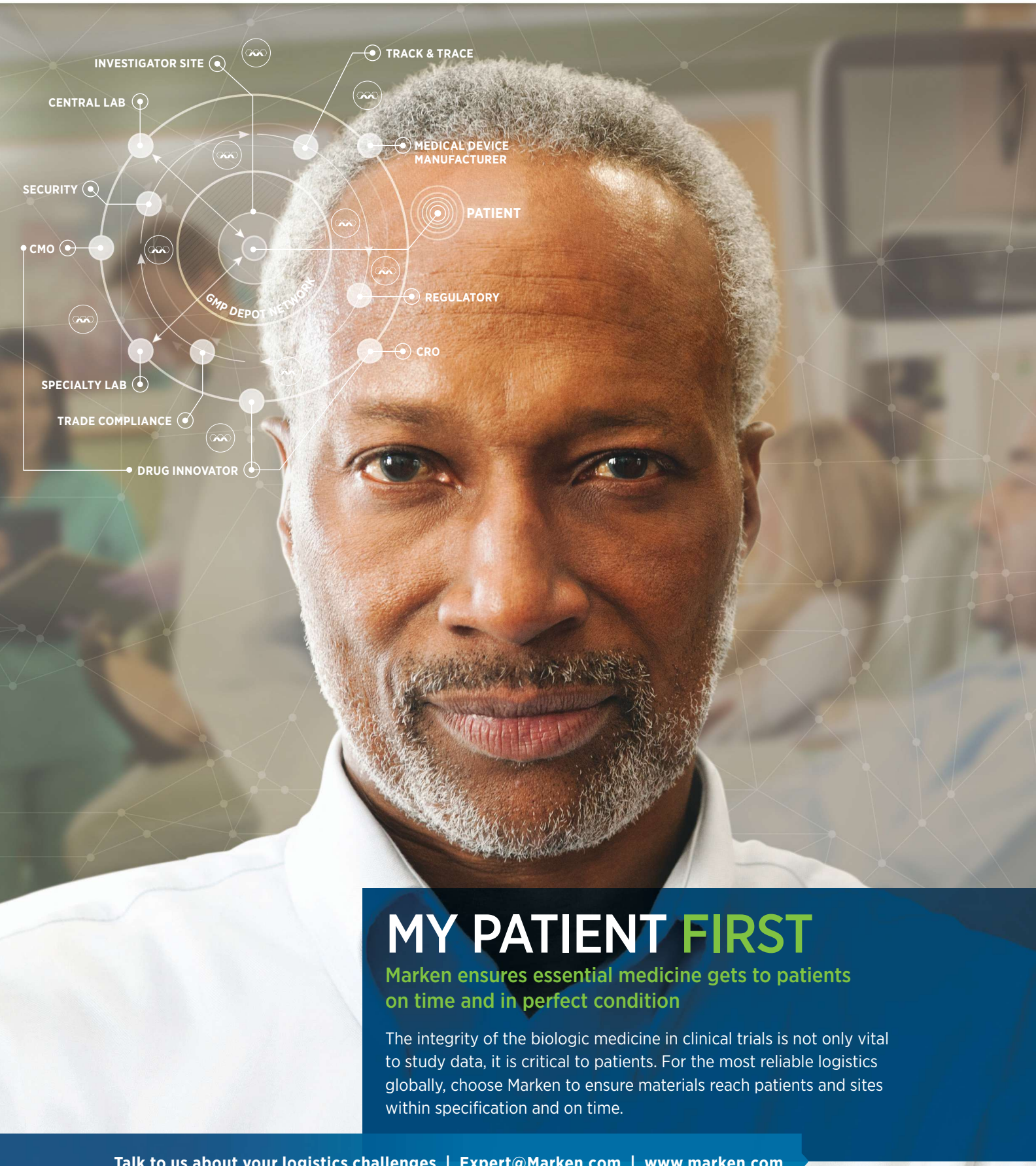

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Learn From Coke When It Comes To Patient-centricity

ROB WRIGHT Chief Editor

During my conversation with Dr. Freda Lewis-Hall, Pfizer's chief medical officer (page 20), she shared an example of one of her employer's products that, frankly, didn't resonate with patients and their lifestyles. Exubera, the first U.S. insulin option approved for type 1 and 2 diabetes that didn't require a needle for administration, was launched in January 2006. Pfizer was so confident Exubera would be a blockbuster, just days before receiving FDA approval the company paid $1.4 billion to Sanofi-Aventis for its share of the inhalable insulin. However, in October 2007, due to lack of consumer demand, Exubera was pulled from the market.

Dr. Lewis-Hall's story on Exubera's flop reminded me of the numerous business marketing cases I studied back at Cleveland State University. Guided by the late Robert Hartley's best-selling textbook, *Marketing Mistakes & Successes*, we dug deeply into the factors behind product feat and failure. As is so often the case, looking back upon marketing botches through the lens of hindsight often reveals leadership decision mistakes that seem blatantly obvious. But are they really? When Exubera was pulled, it was easy for critics to point fingers toward Pfizer's failings (e.g., the drug delivery device was too large). But to me, Pfizer's miss is no more obvious than the famous miscue by the company whose logo has 94 percent global recognition — Coca-Cola.

Back in 1985, the Coca-Cola Company launched new Coke as a replacement to its 99-year-old formula and flagship product. The move was met with an unprecedented firestorm of consumer protests. Company leadership was blasted by pundits for having made the marketing blunder of the century. How could Coca-Cola have made such an obvious mistake? Simple, it wasn't that obvious. At the time, the company had been losing market share in its flagship market with its flagship product for 15 consecutive years. Coca-Cola had to do something to stop the downward skid. By 1984, the company had secretly arrived at a new formula, supported by extensive research. In fact, the $4 million reformulation market research was so solid that then Coca-Cola chairman, Roberto Goizueta, termed the decision to launch new Coke as, "one of the easiest we have ever made." In thousands of blind taste tests, the new formulation not only topped the fabled secret formula, but it also beat out rival Pepsi by 6 to 8 percentage points. Why then did it take just 79 days after the new Coke launch for the original Coke to return to store shelves? Only the benefit of hindsight reveals the company's folly — failing to consider the ability of focus groups to accurately predict the effects of social influence in the real world.

I applaud Lewis-Hall for sharing Pfizer's failure to ask all the right questions of the right patients at the right time when it came to the unsuccessful launch of Exubera. However, if patient-centricity is your goal, all of us can learn from the lessons supplied by new Coke. Their researchers did ask all the right questions of all the right people and yet still failed fabulously — thanks to the ability of Coke loyalists to influence public opinion. Being patient-centric means fully accounting for the ability of players beyond patients to influence public opinion, which can prevent or delay access to even those products clearly deemed superior (e.g., the Cytyc ThinPrep pap test). L

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Q What do you think the Internet of Things (IoT) means as applied to pharma?

A THE INTERNET OF THINGS TO ME refers to everything being connected, and that can be an interesting opportunity in clinical trials. Researchers are increasingly exploring the concept of deep digital phenotyping and the ability to capture robust streaming data from patients. This is starting today with a range of wearables and sensors that are of increasing interest. It is extending into tomorrow to other devices in the home and around the lives of patients to passively capture data and extend the concept of patient-reported outcomes. From medication adherence to quality of life, from activity to physiologic parameters and environmental factors – IoT brings exciting new data. As with all new and large data sources, the ultimate challenge will be in extracting value. The next challenge will be identifying what new analytics capabilities are needed to fully use this new data.

CRAIG LIPSET
Craig Lipset is head of clinical innovation within worldwide R&D at Pfizer. In this role, he works across units and stakeholders to define Pfizer's vision for the future of clinical trials and enables the initiatives and investments to create that future.

Q What is the most valuable lesson you have learned from the shortage of antibiotics in the pipeline, and what can executives and regulators learn and apply to other therapeutic areas?

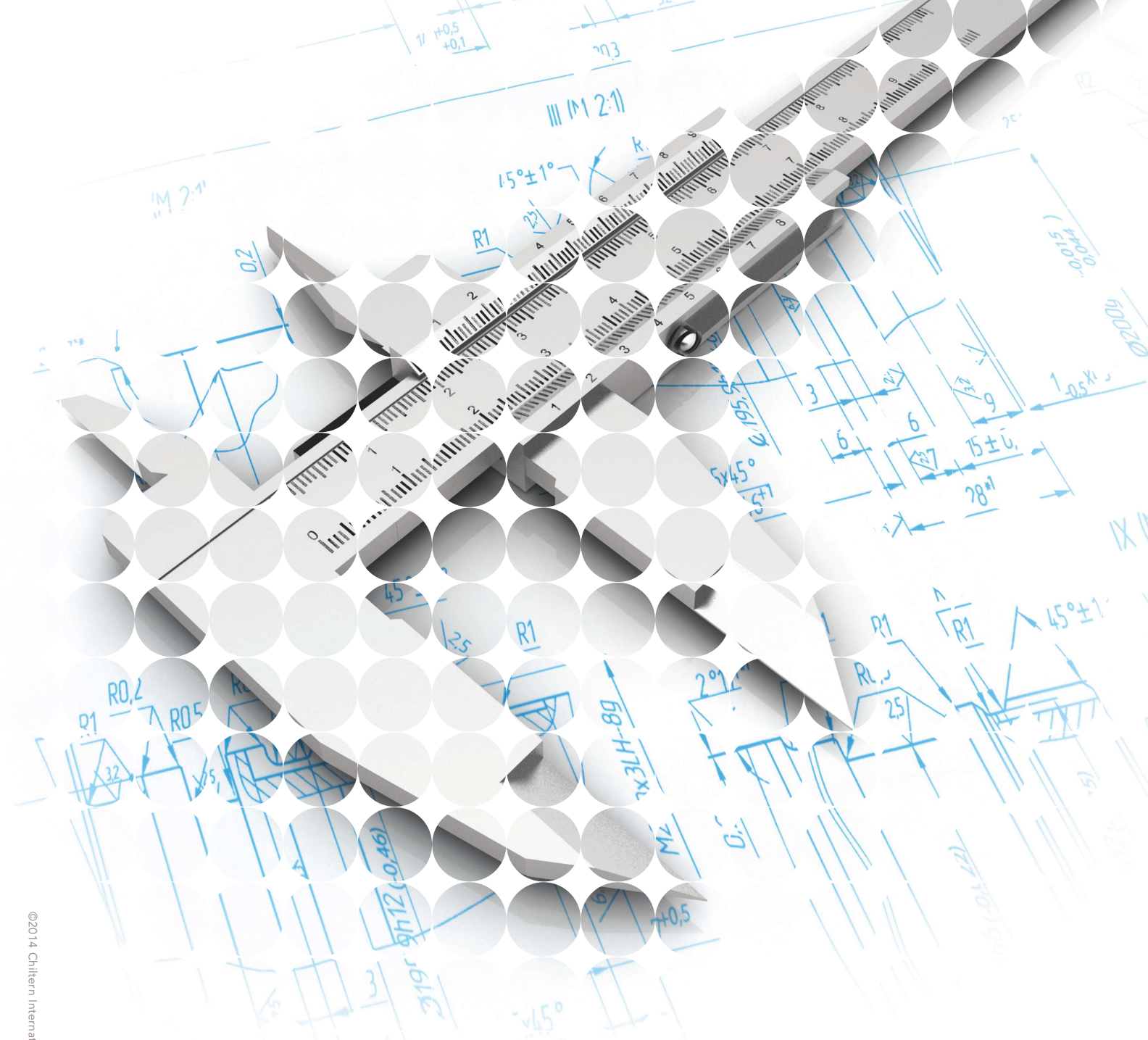
A SUSTAINABLE DEVELOPMENT REQUIRES A STREAMLINED CLINICAL TRIAL PATH, better diagnostics, and pricing and reimbursement that value these assets. Gaining approval for new drugs typically requires that at least two large noninferiority clinical trials have been run. More feasible trial designs are crucial. Currently, no tests can tell physicians which drug may be most useful in treating an infection. We must ensure we have rapid point-of-care tests across therapeutic areas to help medical staff quickly select the right therapies for the right patients at the right time. For antibiotics, the reimbursement process needs to evolve. The model centered on a diagnosis-related group (DRG, or bundled payment system) assuming all patients will respond to the same medicine poses a significant barrier to capturing fair value for antibiotics.

BARRY EISENSTEIN
Barry Eisenstein, MD, FACP, FIDSA, FAAM, is senior VP of scientific affairs at Cubist Pharmaceuticals and editor of *Antimicrobial Agents and Chemotherapy*.

Q What best practices have you seen applied by life science executives when engaging with advocacy organizations, and what practices would you advise them to avoid?

A I RECOMMEND ASSURING YOU ARE ALIGNED with the mission of the advocacy organization. Also, do a "reputation check" to avoid pairing with a group in the center of a storm. Then, seek to find common ground where working together furthers the goals of both entities in a faster, stronger, and better fashion than going it alone. The biggest mistakes I have seen are not gaining sufficient clarity about your desired advocacy outcomes and what you're agreeing to do. There will be a time commitment, so get clarity early on about what is expected of you. Ask for full details about events you need to attend, speeches you're expected to deliver, media in which you may be quoted, and publications in which your writing may appear. This clarity will serve both sides well.

LAURIE P. COOKE
Laurie P. Cooke, BS, RPh, PGDip, CAE, is the CEO of the Healthcare Businesswomen's Association (HBA), a global nonprofit professional association.



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Amnesty Highlights The Inequities Of Obamacare

JOHN McMANUS The McManus Group

Just days after a thorough drubbing in the midterm elections when Republicans wrested control of the Senate from the Democrats, winning almost every contested race and stacking up the largest majority in the House since Prohibition, President Obama announced an executive order that will prevent deportation of 5 million illegal immigrants. Providing amnesty was the president's takeaway from the election?

This unilateral action says more about his intention to work with Congress for the last two years of his presidency than any statement he could make.

But the executive order also highlights the inequities that riddle the implementation of Obamacare. Illegal immigrants in California may soon gain Medicaid coverage that will be financed more than 90 percent by the federal government, while 7 million American citizens who live below the poverty level in 23 states that have not undertaken a Medicaid expansion have no access to coverage. Nancy McFadden, Governor Jerry Brown's (D-CA) top policy aide, recently stated, "We're evaluating, but the president's recent action on undocumented immigrants could perhaps open a door for more coverage of more people under Medi-Cal." California is home to more than one–quarter of illegal immigrants in the U.S.

But much of the South and mountain states have refused to expand Medicaid (see attached map), and Obamacare's legislative language expressly prohibits individuals below the poverty level from obtaining subsidized coverage in the insurance. This decision was made to contain the cost of the program as Medicaid coverage is cheaper than private coverage because it pays providers substantially less. Republicans suggested making private coverage available to all regardless of income, but Senator Mike Enzi's (R-WY) amendment effectuating that change was defeated by Democrats on a party-line vote in the Finance Committee. As a result, in states that have not undertaken a Medicaid expansion, a family of four with income up to $95,400 (that is, four times the poverty rate) can obtain subsidized coverage, but a family below the poverty line cannot. Huh?

In Texas, more than a quarter of the population lacks health insurance, and the poorest of those cannot sign up for subsidized coverage in the health exchange because that coverage is explicitly limited to individuals above poverty. The architects of Obamacare assumed these individuals would get coverage under Medicaid, yet the Supreme Court made that expansion optional for states. But where is the corrective legislation from the administration? President Obama has put nothing forward to address this glaring deficiency with his law, such as repealing the prohibition of subsidized coverage in the exchange for those under the poverty level. He would rather pontificate about state inaction.

These inequities may become even more starkly defined when the Supreme Court rules on *Pruitt v. Burwell* later in June. That case will determine whether Americans living in 36 states who are enrolled in the federal exchange (through the infamously inoperable Healthcare.gov website portal) can continue to receive subsidies for their coverage. If the Supreme Court upholds a logical reading of the statute that subsidies can only flow to an *"exchange established by a state,"* Americans residing in states utilizing the federal exchange cannot receive subsidies, but those enrolled in a state exchange will continue to receive the subsidy.

As a result, a citizen residing in Maryland would retain a full subsidy but a citizen with the identical income living just across the Potomac River in Virginia would not get any subsidy. That is how the law was deliberately drafted, as professor Jonathan Gruber, the key architect of Obamacare, admitted in a now famous leaked video.

Just as baffling, Obamacare's expansion of Medicaid to an additional 9 million poor Americans is facing a new threat: Obamacare itself. Responding to the most fundamental problem with Medicaid — lack of access to physicians willing to accept Medicaid's paltry payments — a recent Department of Health and Human Services Office of Inspector General study found that half of physi-

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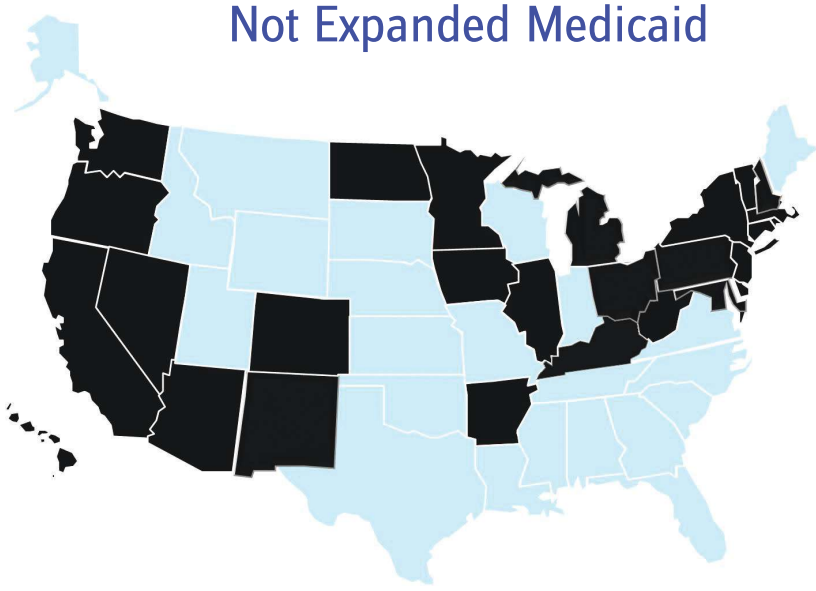
cians listed as serving Medicaid enrollees could not offer appointments to patients. Democrats inserted a provision increasing Medicaid reimbursements to primary care physicians to the Medicare level. This policy resulted in a 73 percent increase in payments, on average, to primary care physicians, according to the Kaiser Family Foundation. Just one problem — the provision lasted for just two years and expired at the end of 2014. Why? It was a budget gimmick to mask the true cost of the program.

Primary care physicians are now just finding out that the enhanced payment was temporary, so many may stop taking Medicaid beneficiaries. This would render the coverage expansion essentially meaningless — if you cannot see a physician willing to treat you, the coverage is in name only. What is the administration's answer to this self-created crisis? Last year's budget suggested a one-year extension of the policy, leaving the identical cliff in the following year. More gimmicks.

Certainly, a Republican Congress could take up the cause and put its own imprint on a policy to address the Medicaid payment-and-access issue by delineating clear metrics on whether a payment enhancement extension is solving the access problem, and perhaps targeting it at the most vulnerable populations to contain costs. But presidential leadership is needed on a program that bears the president's name. Fortunately, 15 states have announced plans to extend the payment enhancement on their own, but failing congressional action, that would establish even more inequities across the country.

Obamacare implementation also has yielded bizarre inequities across populations in terms of covered benefits. Infertility afflicts one out of eight couples and can be caused by medical conditions such as cancer, physical trauma, polcystic ovary syndrome, and endometriosis. Yet infertility treatments were not included in Obamacare's "essential benefits," and the 15 states that presently mandate that benefit will have to pay its full premium cost in 2016 or repeal the mandate.

23 States (shown in blue) Have Not Expanded Medicaid



In these states, 7 million Medicaid-eligible people remain uninsured

Sources: The Advisory Board Company (map) and Families USA (numbers of uninsured)

Meanwhile, Medicare recently determined sex-change operations to be "reasonable and necessary" for Medicare's seniors (average age 76) and will be covered. Federal taxpayers will finance a sex-change for an individual who has lived 80 years as Jane to become Joe, but cannot assist a young couple who cannot conceive because the hopeful mother cannot get pregnant due to chemotherapy or radiation for her cancer. In whose reality does this inequity make sense?

A first step to addressing the emerging inequities in Obamacare is for President Obama himself to recognize and own the current implementation challenges of the law. This means suggesting solutions for the poorest individuals who cannot obtain coverage or see a doctor even if they obtain Medicaid coverage. It also means productively engaging in a real dialogue with Republicans, who will, for the first time in his presidency, control both houses of Congress. Issuing further executive orders and taunting his opposition is no longer a sustainable strategy. 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.

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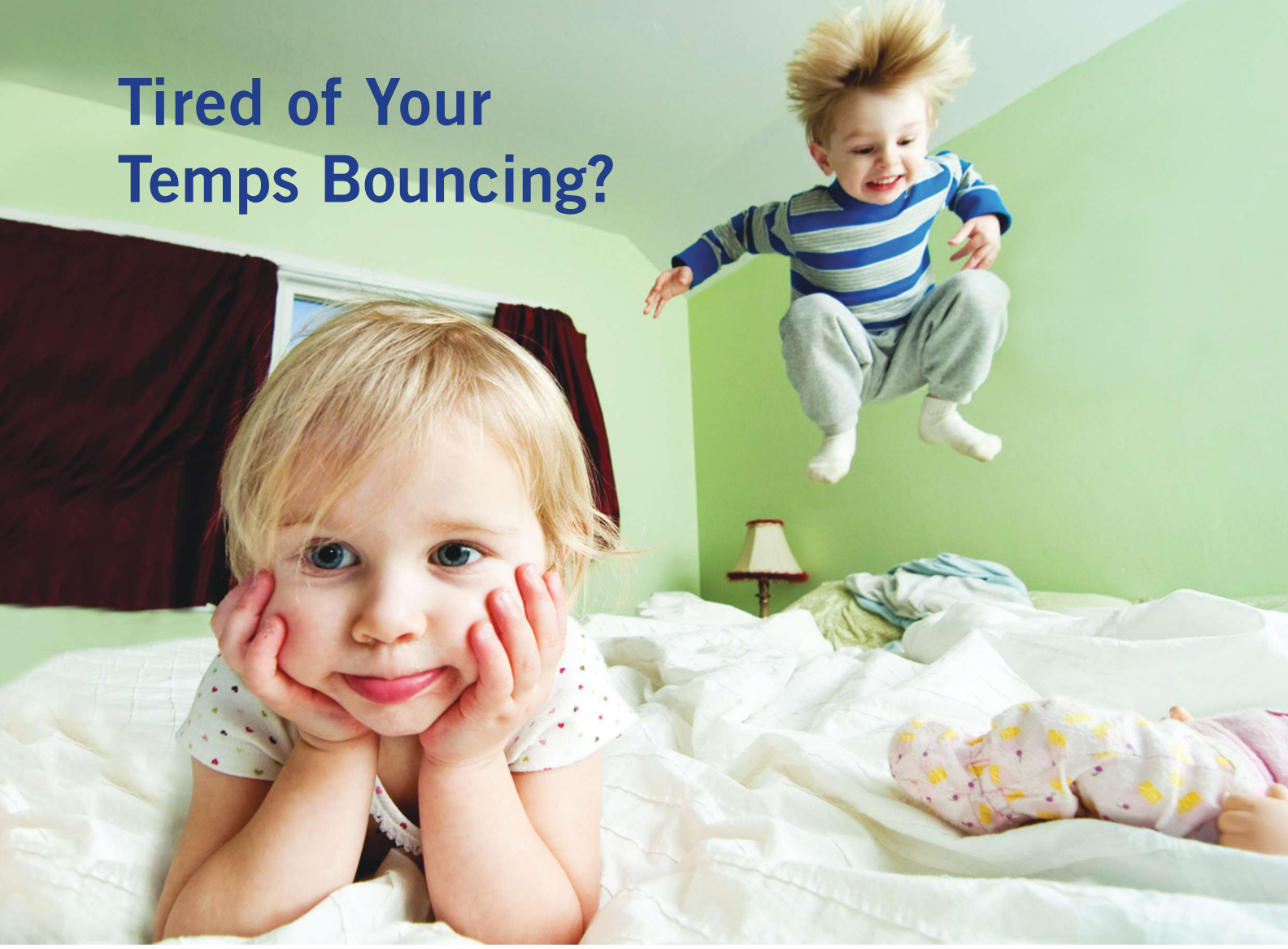

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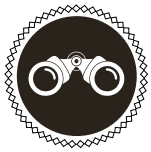

PaxVax

A socially responsible company pushes for global affordability and practical access to its "third-world" vaccines.

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Founded in 2007, expressly "in response to the global threat of the H5N1 pandemic," PaxVax is developing its new vaccine technology "in a socially responsible manner for global impact." Its pipeline includes vaccines for some of the most virulent global threats such as hepatitis, cholera, and typhoid, using the travelers' market to support access to its vaccines in poor countries.

KEY MILESTONES

December 2014: Positive results from Phase 3 safety and lot-to-lot consistency trial of single-dose oral cholera vaccine candidate, PXVX0200. Plans to submit FDA Biologics License Application (BLA) for product (Vaxchora), in mid-2015.

July 2014: Acquired FDA-approved typhoid vaccine Vivotif and Swiss manufacturing plant from Crucell.

WHAT'S AT STAKE

Somewhere "out there," others of our species are suffering strange diseases. Do we care? As a whole, we do not. Or not enough of us do to make a difference at the scale of the afflicted. Only lately has it dawned on the West that those diseases can travel, and they're coming our way. It was once the other way around — our civilization brought plagues bred in European cities to the shores of what would become European colonies. Now, it seems, the tide has turned; visitors from those shores bring new microbial threats to our cities, as do our own international travelers returning home.

You're frightened of Ebola? Meet cholera, typhoid, dengue, flu, and HIV, among other, even tougher customers. What is the ideal protection from those "foreign" threats? In large part, despite vast improvements in treatment, the best solution is still vaccination — vaccination that is practical and affordable for the populations in whom such diseases frequently thrive. That is exactly what attracted me to feature PaxVax in this Companies to Watch edition.

First, I wanted to know why and how the company founders had chosen the mission of pursuing a "double bottom line," balancing the company's financial and social worth — and focusing on affordable oral vaccines for diseases in poor countries. Unlike other companies with a developing-world mission, PaxVax does not wear its altruism on its sleeve. In all respects, the "fully integrated" company reflects the conventional industry background of its experienced management team and well-heeled operations. Its strategy also has a strong practical side — targeting international travelers as a potentially lucrative market to realize its larger goal of overcoming barriers to access in the developing world.

Of course, the most important reason to keep an eye on PaxVax over time is to see how well it hews to the larger mission if it succeeds in the travelers' market. A cynic could easily envision the company getting too comfortable with cushy revenues and profits, and putting off the perils of the developing world indefinitely. If it only were to realize the holy grail of stable, oral, and low-manufacturing-cost vaccines, however, the gates (meaning no pun) would be open. A huge barrier to access would indeed have fallen, and we would make a giant step toward dealing with the grim travelers of disease crisscrossing the planet daily.

PaxVax says the Phase 3 trial of its cholera vaccine candidate, involving about 3,000 participants in Australia and the United States, evaluated the immunogenicity and safety of three consecutive production lots, all of which induced immunological responses meeting the planned endpoint for manufacturing consistency. The company produced the test lots at its facilities in San Diego and newly acquired plant in Bern, Switzerland. L

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Innovation Moves Up In Rank And Technologies Move Into The Outsourcing Paradigm

Now into the fifth year of examining outsourcing behaviors and ways contract suppliers can improve the drug development process, the results from the 2015 Nice Insight Biopharmaceutical Outsourcing Survey show that the biopharmaceutical industry is making some subtle changes in how it prioritizes companies when it comes to selecting a CRO or CMO.

KATE HAMMEKE
Director of Marketing Intelligence
Nice Insight

"Respondents indicated that safety topped the list of how technological innovations would influence outsourcing partner selection."

For the first time since introducing the measure in 2012 (when it replaced "accessibility"), innovation moved up in rank among the six key outsourcing drivers to tie for fifth place with a company's regulatory track record. Introducing innovative new technologies to the lab, manufacturing plant, or supply chain can boost productivity and strategically position your business to attract projects that utilize these assets.

Almost two-thirds of research participants stated that they had learned of a technological innovation in the past year that would benefit their company (62 percent). Respondents indicated that safety topped the list of how technological innovations would influence outsourcing partner selection, followed by efficiency and security. Interestingly, patient-centric traits tended to place higher in the ranks than technological innovations that were more in tune with the business' profits like creating customer loyalty, speeding time to market, or improving traceability. The areas to experience the greatest benefit from technological innovations were quality control, research and development, and manufacturing; this shows that both CROs and CMOs have an opportunity to capture new business and partnerships by promoting innovative technologies utilized by the company. As a matter of fact, interest levels in partnering with a CRO/CMO utilizing technological innovations for increased efficiency, quality, safety, and traceability were very strong — only 3 percent of respondents indicated no interest.

Not only has innovation moved up in ranks when it comes to factors that influence outsourcing partner selection, so has productivity, which ranked fifth in 2013, fourth in 2014 and now third in 2015. Improving time to market through increased productivity is a key way technological innovations can provide an advantage, especially when it comes to contract research. Sixty-two percent of respondents stated that cloud-based data management services were the greatest opportunity for cost and/or timesaving when it comes to contract research. This was followed by half of respondents stating that the use of robotics labs to perform routine tests would improve productivity. Web-based life sciences labs were supported by 44 percent of respondents, and both mobile technologies for recruiting/communicating with participants as well as mobile technology for monitoring

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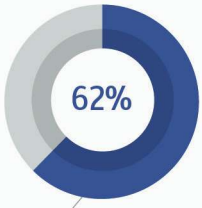
FIGURE 1 Rank Of Industry Drivers

	2012 - 2013	2013 - 2014	2014 - 2015
Quality	1	1	1
Reliability	2	2	2
Productivity	5	4	3
Affordability	4	5	4
Regulatory	3	3	5
Innovation	6	6	5

FIGURE 2 Technological Innovation Awareness



Percentage of respondents who have learned of new technological innovations for the biopharma industry in the past year that would benefit their company

FIGURE 3 Increased Technological Innovation Would Benefit The Following Areas

Quality Control	1
Research & Development	2
Manufacturing	3
Distribution	4
Labeling / Packaging	5

FIGURE 4 Categories Of Technological Innovation That Influence Outsourcing Partner Selection

1 Safety	2 Efficiency	3 Security	4 Regulatory Compliance
5 Patient Compliance	6 Speed	7 Loyalty	8 Traceability

Survey Methodology: The Nice Insight Pharmaceutical and Biotechnology Survey is deployed to outsourcing-facing pharmaceutical and biotechnology executives on an annual basis. The 2014-2015 report includes responses from 2,303 participants. The survey is comprised of 240+ questions and randomly presents ~35 questions to each respondent in order to collect baseline information with respect to customer awareness and customer perceptions of the top ~125 CMOs and ~75 CROs servicing the drug development cycle. Five levels of awareness, from "I've never heard of them" to "I've worked with them" factor into the overall customer awareness score. The customer perception score is based on six drivers in outsourcing: Quality, Innovation, Regulatory Track Record, Affordability, Productivity, and Reliability. In addition to measuring customer awareness and perception information on specific companies, the survey collects data on general outsourcing practices and preferences as well as barriers to strategic partnerships among buyers of outsourced services.

participants were backed by 38 percent of respondents. Shared online data banks for nonproprietary clinical information rounded out the list with 23 percent of respondents indicating it as an opportunity for cost and/or timesaving.

While a robotics lab may sound like it's right out of a sci-fi film, the technology currently exists and has the potential to offer a variety of advantages to drug developers. According to survey respondents, the most appealing element of working with a robotics lab is that it can offer faster turnaround than a traditional CRO due to its 24/7 workflow (61 percent). More than half of the respondents found the reduced possibility of human error (56 percent) and the precise nature of repetitive tasks making the experiments more easily reproduced (50 percent) to be benefits of engaging a robotics lab. The mechanical advantage of using robots may give way to secondary benefits like freeing up staff from rote tasks so that scientists can focus on data interpretation and designing new experiments (41 percent).

It will be interesting to see how businesses like Transcriptic and Emerald Cloud Laboratory—two potential game changers based out of Menlo Park, CA — will fit into the outsourcing strategies of drug developers. Regardless of how these innovative companies are included in the mix, one thing is for sure: Biopharma companies are drawn to contract suppliers that use innovative technologies to improve productivity. L

N. WALKER

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

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Pfizer: Putting The Patient At The Center Of Its Drug Development UNIVERSE

ROB WRIGHT

I FIRST MET FREDA LEWIS-HALL, M.D., ON MAY 5, 2011, IN NEW YORK.

Pfizer's chief medical officer had just concluded her Healthcare Businesswomen's Association (HBA) Woman of the Year (WOTY) acceptance speech in which she challenged attendees to recommit, reenergize, and reform themselves to "be everything the patients we serve need us to be, and then some."


FREDA LEWIS-HALL, M.D. Chief Medical Officer at Pfizer

As we fast-forward nearly four years, her words seem even timelier today. And while much has evolved in healthcare since the delivery of her memorable message, one thing that hasn't is patient need — a point punctuated by the shrill of an ambulance siren whirring past the chief medical officer's East 42nd Street New York office.

During today's discussion, Lewis-Hall states that, "In our medical organization, the patient has always been our North Star." And though Pfizer has been implementing patient-centric programs and platforms for years, it wasn't until 2013 that the company took patient-centricity on as a named strategy. Leadership realized that to better enable patient engagement throughout the entirety of the drug discovery, development, and delivery process, the company needed to be more systematic. "As an organization, we needed to organize our patient-centric thinking, systems, and processes to make it consistently part of what we do every day," she states.

To Become Patient-Centric Requires Learning, Listening, And Collaborating

One of the first steps Pfizer took toward getting organized around patient-centricity involved — and still involves — learning and listening. "Our teams are looking for opportunities to understand better what patients, caregivers, and patient advocates can share as insights to help us clarify their needs, and then to help us better meet them or to problem-solve," Lewis-Hall states.

While some of these insights have been gained through positive experiences, she admits others have been learned through Pfizer misses. "Exubera would be a good example," she says. The first U.S. insulin option indicated for type 1 and 2 diabetes not administered via injection (it was an inhaled insulin), Exubera received FDA approval in January 2006. However, this once-anticipated blockbuster was withdrawn from the market in October 2007. Its removal was not the result of drug safety concerns, but the lack of consumer demand. "This amazing science, incredible engineering, and true breakthrough frankly did not resonate with patients and their lifestyle," Lewis-Hall says. "We realized we hadn't asked all the right questions of the right patients at the right time, and yet we continued pushing forward." As a result, Pfizer took a $2.8 billion charge when it wrote off the drug, including $661 million of Exubera inventory.

One of Lewis-Hall's favorite examples of a Pfizer miss turned patient-centric opportunity occurred shortly after she joined

Don't Miss The Opportunity To Balance Your Social Media Equation

Just about every biopharmaceutical company has a presence in social media. Pfizer is no different. According to the company's chief medical officer, Dr. Freda Lewis-Hall, the company now uses social media in two ways. "One is to help get information from patients," she states. "We have a great example with our Get Old platform. It allows us to be part of an organically grown conversation about people and their attitudes toward healthy aging."

The second use for social media is to provide patients with information on timely topical issues. "Through our Get Healthy, Stay Healthy site, for example, patients are able to connect with our medical information group and ask questions about diseases, wellness, and prevention. They end up sharing information with us, such as how they feel about the topics we've covered. The questions patients have are just as informative as their willingness to actively engage."

While social media has a lot of upside to improve biopharma patient engagement, there is another side to it, with which Lewis-Hall admits Pfizer is grappling. "The potential of social media to have a negative impact in the clinical trial environment is fairly significant," she affirms. "For example, what happens when patients are blogging about their experience in a clinical trial, trading tricks about how to get into a trial, sharing information about how they feel or what they are experiencing during the trial, and whether or not they think they're on the standard of care, placebo, or the new experimental product?" Obviously, these kinds of issues could affect everything from patients' willingness to participate to how and what they report about their own experiences to an investigator. Nevertheless, Lewis-Hall believes social media represents an opportunity for companies to do more than just make clinical trials better or more accessible for patients. It can also help to educate and interact with clinical trial participants to help them understand the potential negative consequences of online conversations. "Interrupting the conduct of a clinical trial can prevent new treatments from getting beyond the trial and into the hands of patients who need them," she attests. While she understands many of these conversations are meant to be helpful, they need to be conducted in such a way as to minimize the risk to the trial. If you want to get the most out of using social media as a patient engagement tool, Lewis-Hall suggests striving to educate beyond diseases, products, treatments, and trials.

the company. "It was an 'aha' moment for me," she recounts. "Patients volunteer for our clinical trials, travel many miles, spend hours devoting themselves, and are committed to the work we do. At the end of the trial, we say 'bye-bye,' often without as much as a thank you." To rectify this rather nonpatient-centric approach, a member of the Pfizer team tested the notion of establishing a platform that would thank clinical trial volunteers, as well as provide them the opportunity to get summary results from the trial. "In this way, they understood what their hard work and commitment had won in terms of advancing science around the disease," Lewis-Hall attests. In addition, by providing a platform to stay connected to Pfizer, patients naturally began to take a more active and engaged role in the field of drug development. Now known as Pfizer Link, Lewis-Hall describes this online community as a key patient-centric engagement tool and a "clinical trial alumni association" for people who have graduated from a Pfizer clinical trial. Participants are given access to current information on diseases and conditions of interest, including suggestions and tools for disease management, opportunities to participate in future clinical trials, and registries.

As for patient-centric lessons learned, Lewis-Hall references collaborations such as the $58 million agreement between Pfizer and the Cystic Fibrosis (CF) Foundation to discover new treatments for people with the most common mutation of CF (Delta F508), and Lung-MAP, a lung cancer master protocol trial. "These are full-on meta-collaborations," she affirms. "Lung-MAP includes the NIH through the NCI [National Cancer Institute], the FDA, Friends of Cancer Research, and five companies [Amgen, Genentech, Pfizer, AstraZeneca, and AstraZeneca's global biologics R&D arm, MedImmune]. It's also fully integrated to include patient input from beginning to end." Lewis-Hall believes these meta-collaborations demonstrate that patient-centricity is not an activity for biopharma companies seeking a competitive advantage, but a presage of a new norm for how industry and regulators can and should operate. "The FDA has fielded a series of patient-centric public meetings, and the EMA [European Medicines Agency] has pilots to include patient input to the CHMP [Committee for Medicinal Products for Human Use] on benefits vs. risks," she states.

Capture Your Existing Patient-Centric Best Practices

If you are like Pfizer, you have developed and implemented patient-centric initiatives guided by patients. But how are you capturing these best practices so you can replicate them? "We saw various leadership-championed initiatives growing throughout Pfizer as best practices," Lewis-Hall testifies. "But in a place this

size and with so much going on, we realized continued success meant putting some structure around it." In 2014, Pfizer created the office of global patient affairs. Headed by Roslyn Schneider, M.D., this group is charged with collecting, synthesizing, developing, and implementing a framework to better involve patients across all of Pfizer. This framework (i.e., structure) is designed to build "capabilities, systems, processes, and platforms for sharing in order to make this a part of everyone's day," Lewis-Hall says.

To better understand the type of information this group is trying to capture, Lewis-Hall shares two examples, the first of which is related to Xeljanz (tofacitinib), the company's compound for rheumatoid arthritis. Xeljanz originally received FDA approval for rheumatoid arthritis in November 2012. A year later, the FDA approved a supplemental new drug application (sNDA) including additional patient-reported outcomes data. Says Lewis-Hall, "We worked to include things that are not usually part of a clinical trial." As examples, she lists the eight domains (i.e., vitality, role physical, role emotional, physical function, bodily pain, social function, mental health, and general health) of the Medical Outcomes Study Short-Form (36-Item) Health Survey (SF-36) used on the Xeljanz sNDA that now appear in the label. "That's a soup-to-nuts example of listening to patients about what's important to them, including it in clinical trials, collecting and analyzing the data, and then sharing it back with the patient community."

For the second example, Lewis-Hall references Pfizer's fieldwork on understanding smoking cessation. "What are the differences between smokers and patients who'd like to quit?" she asks. "How do you define someone who's ready to quit or who's not? How do you understand what drives the urge to smoke?" To better understand these questions, the Chantix (varenicline) team used validated scales and a brief questionnaire that clarified smoking urges. They also used a withdrawal scale explaining what kinds of symptoms people experience when withdrawing from nicotine. "These were included as part of the supportive prescribing information, and are two examples of responding to what patients say they care about when considering their options," she says.

Questions To Ask When Becoming Patient-Centric

If your goal is to make your organization more patient-centric, Lewis-Hall suggests asking the following questions: "How do you take the desire on the part of patients to be able to tell you what's important to them? How do you identify or develop tools to collect this information? How do you ensure their validity or go about validating? How do you utilize the tools? How do you communicate the information back to patients, while systematically teaching the different teams working across other areas in your organization?"

She adds that the key to being patient-centric isn't just finding and using patient-centric tools, but understanding when they are appropriate to deploy. Ruminate on the following example: "We had some special challenges in a sickle-cell disease study," she states. "This is an emergency-room-based study where patients have to be in crisis. It's a unique population, many of whom have been ill all their lives and are experiencing agonizing pain." In trying to figure out how to meet these patients' needs while creating a manageable study, Pfizer deployed tools not often used in the clinical setting, such as ethnography and medical anthropology. "We worked with the physicians, patients, and advocates so they all better understood and articulated the patient's journey," Lewis-Hall shares.

How Patient-Centric Are You?

You are probably curious about what metrics Pfizer uses to measure the success or failure of its patient-centric best practices. Lewis-Hall says the first important metric is reach, which is measured by determining which of the company's programs are deploying

Try Nontraditional Research Approaches

Patients often struggle to communicate via surveys and focus groups as to what is really important to them. This makes creating patient-centric initiatives difficult.

To better capture the true user experience, Pfizer's consumer health group (makers of products such as ChapStick, Robitussin, and Advil) employs a rather unique tool. "We have a model home in the U.S. where we do research," explains Pfizer's chief medical officer, Dr. Freda Lewis-Hall. This tool helps Pfizer employees better understand what actually happens when company products get into the hands of consumers. While it's not often used in the pharma space, Lewis-Hall thinks the concept of observing user experience may have some applicability. For example, in Europe Pfizer has a similar dedicated user-experience observational space. "We've been bringing patients and caregivers in, giving them some medical software, and through observation, seeking to better understand their experience."

Another patient-experience mechanism involves the recently signed research agreement between Pfizer and the personal genetics company, 23andMe. "We hope to enroll thousands of patients who have inflammatory bowel disease [IBD]," Lewis-Hall states. By studying genetic factors and severity of symptoms over the course of illness, as well as responsiveness to therapy, Pfizer employees anticipate gaining a deeper understanding of individual IBD patient variability. "This is an example of leveraging technology so we can better characterize patient disease subgroups, helping us to think about what patients might best benefit from one intervention versus another," she says. Lewis-Hall believes that if you want to better understand the patient, you need to be willing to try some nontraditional research approaches.

patient-centric systems developed by the company. "Over time we want to see more of the organization deploying what we believe to be successful strategies that include patient input."

Another key metric is patient engagement, and she says there are a lot of ways to measure this. For instance, you could measure how many patients are using tools developed by Pfizer, such as mobile apps. "We have an app in Australia where patients can have prescribing information on their cell phone and the immediate ability to click through to our medical information centers with either a call or an email in case they have questions," she relates.

Another patient engagement measure Pfizer considers is the number of patients using the Blue Button technology launched by the U.S. Departments of Veterans Affairs and Health and Human Services that enables Pfizer trial participants to download their own electronic clinical data collected in the trial. Pfizer also considers the number of patients enrolling on Pfizer Link and the number of questions being submitted through the company's Get Healthy, Stay Healthy portal. But just measuring engagement is not enough. Lewis-Hall says the company is also seeking to measure satisfaction after engagement. "We ask what patients thought about the information they received," she states. "Did it satisfy your needs? Would you come again for more information?" According to Lewis-Hall, engagement satisfaction is a measurement you should be doing continuously.

One of the metrics most exciting to the Pfizer team is the intent to act. Instead of just measuring how many patients asked for and were given information, Lewis-Hall says the intent to act is one of the best measures of effective engagement. "If I talk to you about how to stay healthy if you have diabetes and have to travel overseas, your intent to act becomes an important opportunity for us," she states. "We're tracking and using that feedback as direction for improving engagement." If you are using patient input to help shape clinical trials, you should measure how many protocol changes there are over time and compare that number to similar trials that didn't have patient input. "Want to measure how well you are listening or meeting patient needs?" Lewis-Hall asks. "Compare the number of patient suggestions to how many you actually incorporated." Pfizer's chief medical officer advises to make sure you are matching the correct tool with the correct target. "We have measures for pre-study, in-study, post-study, and in-market or in-community to determine if we hit the mark," she clarifies.

Finally, don't use the excuse "We are a small or virtual company and outsource everything" as rationale for why you don't have to or can't implement or measure patient-centric programs. "Our model isn't outsourced as much as it is partner-sourced," Lewis-Hall explains. "From the very beginning, we have the opportunity with our partners to align, gain agreement, and confer our concerns, enthusiasms, and mechanisms for patient engagement from inside the Pfizer walls to all the people who help us do the work outside the walls of Pfizer as partners and collaborators." In other words, if you want to put the patient at the center of your drug development universe, take an active role in developing, adopting, capturing, and measuring your patient-centric initiatives — even if you are in a fully outsourced model.

Patient-centric Means Going To Where The Patient Is

In the early 1960s, approximately 40 percent of U.S. doctor-patient meetings were conducted in the home. By the 1980s this number had dropped to under 1 percent. There are a number of reasons for why the "house call" fell out of favor, including time inefficiency, inconvenience, and lack of needed medical equipment. But becoming patient-centric requires a willingness to go where the patient is. While new apps and technologies are helping the "house call" make a comeback, one media platform Pfizer is using to go where patients are is television. "We started with the CBS-syndicated show *The Doctors* as a platform for engaging with the public where they sit, in ways they are accustomed to and comfortable," says Pfizer's chief medical officer, Dr. Freda Lewis-Hall. Since this initial foray, the concept has migrated to include the number one-rated syndicated daytime television talk show, *Dr. Phil.* According to Lewis-Hall, this TV platform is highly integrated with Pfizer staff involvement by Dr. Phil to provide viewers with timely medical information and help connect consumers with additional resources (e.g., Get Healthy, Stay Healthy).

Lewis-Hall learned the power of television as an educational tool early in her career. Living in Washington, D.C., she participated in a medical education program for PBS. About three weeks after the airing of an episode on diabetes, she was approached by an older gentleman while grocery shopping. "Ain't you that young child on television," she recalls him inquiring. He proceeded to inform Lewis-Hall how he had seen her on TV, and as a result, had gone to see a doctor about his condition. "Sure enough," he said, "I had a touch of sugar." Her stated goal prior to doing the show was to get one patient who didn't know they had diabetes to learn about the condition and take action.

For Pfizer's chief medical officer, being patient-centric means not only going to where the patient is, but doing so one patient at a time. "My earliest learning was with a patient," she recollects. "Thirty years ago, I was using data and statistics to help inform a patient." About midway through the talk where Dr. Lewis-Hall had been explaining what typically happens to the average patient, the woman looked at her and said, "You know what? I'm not average, I'm me." TV, social media, and other patient-centric initiatives are all engagement tools. "The learning is that patient-centricity is a long road, not all patients are the same, and we are going to need to develop a pretty big toolbox to really meet their needs overall."

COMBINATION CANCER IMMUNOTHERAPY — A VIRTUAL ROUNDTABLE

A SERIES ON THE CHALLENGES AND OPPORTUNITIES OF USING NEW AGENTS TO RALLY THE IMMUNE SYSTEM AGAINST CANCER

WAYNE KOBERSTEIN Executive Editor
LLEW KELTNER, M.D., Ph.D. Roundtable Moderator

In the end, there were too many responses, too many willing participants, for our virtual roundtable to include them all. We end our Combination Cancer Immunotherapy series with this final installment, Part Five, featuring input from four of the hottest companies in the field: Merck & Co. (MSD, outside North America), Five Prime Therapeutics, Heat Biologics, and OncoSec. Editorial space considerations demand a finale to the series, leaving out at least eight of the two dozen companies that submitted discussion responses and more expressing interest. Our apologies to those companies, to whom and for whom we owe some explanation.

Our final selection reflects a simple criteria: We chose companies with a range of technologies and at various stages of development, whose immunotherapies directly target the immune system primarily by altering immune cells, as do the checkpoint inhibitors. (One semi-exception, OncoSec, has an intratumoral therapy designed to be synergistic with checkpoint inhibition.) Plenty of other approaches can claim some immunotherapeutic action by targeting the tumor antigens or microenvironment. But the number of candidates and alternative mechanisms of that sort is now proliferating beyond our ability to do anything but show some examples. At some point, we had to decide when to call an end or go on forever publishing company responses.

PART FIVE: A WRAP: HOW DO THE KOLs & COMPANIES COMPARE?

To date, we have given a good account of the concepts and applications, theory and reality, of cancer immunotherapy. Parts One and Two thoroughly shared the range of views among key opinion leaders. The subsequent parts have covered companies' real-world experiences trying to apply the concept in a business environment. Each company is unique in its practical views and approach. Every one holds lessons for any life sciences company taking on the risks and responsibilities of developing highly innovative products. We conclude Part Five and the series itself with the moderator's summary of concepts and lessons discussed in the virtual roundtable as a whole.

The companies here continue to assess the reasons for using cancer immunotherapies in combinations, the criteria by which the combination components are likely to be selected, the business models most likely to prevail, and the key challenges in commercializing and delivering cancer immunotherapies to real patients in the real world. Candidates for "backbone" therapies, personalized versus off-the-shelf treatments, and alternative combinations also enter the discussion. (See also "Questions Verbatim" in Part Four, December 2014.)

MERCK
(Known as MSD outside the United States and Canada)

Now marketing an FDA-approved PD-1 inhibitor, Keytruda (pembrolizumab) for advanced melanoma, Merck is pursuing a broad research and development program in immuno-oncology with Keytruda leading the company's research efforts.

ERIC RUBIN, M.D.
Vice President,
Oncology Clinical Research

WHY COMBINATIONS?
Combinations should be studied, but in certain patients a single agent will be sufficient. That is shown by our data in melanoma, where many of our responding patients have remained in remission at the two-year mark. Though they are not a majority of patients, it is a significant portion. For those patients, there may be no need for additional agents, and that will probably be true of other cancers as well.

ESSENTIAL COMPONENTS?
The notion of combination therapy in cancer is not new, and the lessons from that longtime standard of care can help guide choices of combinations in immunotherapy. Mechanism-based combinations should be prioritized. Given our understanding of the PD-1/PD-L1 pathway, what are the logical drugs we should bring in to combine with an agent like ours? We would need agents that contribute to the synergistic improvement in efficacy of the anti-PD-1 drug without a lot of additional toxicity. There are a number of companies now developing other immunotherapy approaches they believe will be complementary to our agent, and I spend a lot of time talking with such companies. The focus in cancer now is on immunotherapy, as it has been with other areas such as molecular-pathway targeting.

BACKBONE THERAPY?
I do believe anti-PD-1/PD-L1 will be the backbone approach for some time to come. With the extraordinary results we have seen with these agents — many now have breakthrough designations as we do with pembrolizumab in melanoma and lung cancer — it does not seem likely in the near term something else will come in to displace anti-PD-1/PD-L1. There are other checkpoint inhibitor targets under investigation; maybe in a number of years we will see something with results that eclipse those we have with our approach, but for now that is unlikely, and anti-PD-1/PD-L1 will be the backbone immunotherapy.

COMBO CRITERIA?
Although our understanding of the mechanisms of PD-1/PD-L1 in patients is limited, there is an increasing knowledge in this space that would allow rational, mechanism-based decisions on what to include in combinations. That would primarily be other immunotherapies, but there is increasing data that other agents such as chemotherapies can alter the tumor microenvironment in advantageous ways for an anti-PD-1 agent, increasing the immuno-antigen repertoire. Epigenetic inhibitors might also be attractive candidates. That said, some of our best combinations in cancer treatment were discovered somewhat empirically. So we and others will take a broad approach to looking at combinations. Much of this will have to be sorted out in the clinic and in randomized clinical trials.

Biomarkers add another level of complexity. We are interested in applying PD-L1 as a biomarker, because higher levels of PD-L1 expression correspond to higher levels of response, though it is clear some patients with low PD-L1 expression also respond. Our registration trials in lung cancer use an "enrichment design," which requires some PD-L1 expression in the tumor for the patient to be eligible. There is an analogy to Herceptin, which may not have ever been approved without use of the HER-2 biomarker in its pivotal trial — to ensure maximum benefit in the selected patient population. That can accelerate initial approval; then we can go back and understand whether we can extend use of the drug to some patients with low biomarker levels. We are also investigating other biomarker technologies as well, such as DNA or RNA-based biomarkers.

NARROW OR WIDE APPLICATIONS?
With our drug, like others, we are finding there are patients with every cancer type who respond. Again, although it is not 100 percent of patients, it is clear that even a single agent is capable of having a response in individual patients with a wide variety of cancer types.

FIVE PRIME THERAPEUTICS

Preclinical development of immunotherapies in cancer and other areas.

BRIAN WONG, M.D., PH.D.
Vice President, Research and
Head of Immuno-Oncology

WHY COMBINATIONS?
Tumors are thought to frequently upregulate multiple immune checkpoints to escape destruction by the immune system, and for that reason, it may be more efficacious in many tumor settings to use combinations of immunotherapies. Indeed, early clinical data with ipilimumab plus nivolumab (anti-PD-1) suggest that the combination is more effective than ipilimumab alone in the treatment of advanced melanoma. Five Prime will initiate a clinical trial next year combining FPA008, our antibody targeting tumor-associated macrophages (TAMs), with BMS's nivolumab in six cancer indications. TAMs are emerging as key cell types that suppress antitumor immunity.

ESSENTIAL COMPONENTS?
This will be specific to each patient's tumor, and molecular profiling of the dysregulated immune checkpoints will likely be needed to determine the optimal combination regimen of immunotherapies to use against the specific cancer in that patient. Two or more checkpoints could be targeted simultaneously by multiple drugs with single specificities, or drugs with multiple specificities such as bispecific antibodies could be developed. In

addition, combinations of immune checkpoint inhibitors with other mechanisms such as cancer vaccines, cell therapies, and immune-activating antibodies are now being tested in the clinic and will likely be part of the oncologist's armamentarium in the future.

BACKBONE THERAPY?

It is probably too early to tell whether one axis will be the backbone of all immuno-oncology combinations. There will be variability from tumor type to tumor type and even among patients. Already, data suggest that the CTLA-4 and PD-1/PD-L1 pathways are more relevant for drug therapy in some tumors than others. Our understanding of therapeutic selection will become more refined as the roles of particular immune checkpoints are better elucidated across a wide range of tumors. Five Prime is developing novel checkpoints that could be used in combination with the clinically validated pathway inhibitors, but may also be used as a single agent in tumors that do not respond well to those therapies.

COMBO CRITERIA?

Selection of specific immuno-oncology combinations will likely be done by characterizing immune checkpoint proteins (or the nucleic acid transcripts that code for such proteins) present in a patient's tumor or immune cells. In addition, the safety profile of each drug should be considered before combining them.

NARROW OR WIDE APPLICATIONS?

Five Prime focuses on more generalizable immuno-oncology approaches that can be given to all patients who are likely to have the relevant target for a drug such as a monoclonal antibody. However, this doesn't mean that we can ignore what the patient's tumor looks like. As patients, physicians, and payers demand better outcomes and probabilities of success, there will be demand for biomarker molecular profiling to select immunotherapies most likely to result in durable responses and improved survival.

PERSONAL OR BROAD?

Patient cell-based approaches, such as artificial T cells expressing tumor-recognizing receptors (also known as chimeric antigen receptor-T cells, or CAR-T cells), are intriguing, and some of the Phase 1 data, particularly in hematologic malignancies, have been exciting. The CAR-T cells are reintroduced into the patient and hopefully recognize and kill the cancer cells. So every patient represents essentially a separate manufacturing lot. Despite encouraging data, significant

safety and logistical issues remain. Other individualized therapies that may emerge include cancer vaccines, in which the patient's own tumor antigens are used to boost the immune response.

For cancer immunotherapies that are monoclonal antibodies, the limits will be the traditional ones of safety, efficacy, approved indications, payer coverage, and convenience and tolerability. For cell-based approaches, given their inherent logistical complexity and safety risks because they cannot be easily turned "off," they may be initially reserved for patients in intensive-care or salvage settings, at least in the near term.

GENERAL COMMENT?

Many key opinion leaders believe we have only just scratched the surface in identifying mechanisms that enable the immune system to kill tumor cells. One of the key factors hindering the discovery of the next generation of immunotherapies is the lack of mechanistic understanding of immune dysregulation in tumors. Many known checkpoint regulators do not have identified ligands. This makes drug development, rational selection of combinations, and companion diagnostic development very difficult. In addition, it is likely that many pathways that control the immune response in tumors remain to be discovered. Technologies that can uncover these ligands and pathway information will provide a competitive advantage in the field. A priority will be to work out how immunotherapies combine or do not combine with established standards of care for various cancers, as well as other immunotherapies.

> "IT MAY BE MORE EFFICACIOUS IN MANY TUMOR SETTINGS TO USE COMBINATIONS OF IMMUNOTHERAPIES."

BRIAN WONG, M.D., PH.D.
Vice President, Research and Head of Immuno-Oncology
Five Prime Therapeutics

HEAT BIOLOGICS

Developing ImPACT Therapy — A First-In-Class Fully Human Cytotoxic T Cell-Specific Immunotherapy.

JEFF WOLF
Founder and CEO

WHY COMBINATIONS?

While it is possible to envision a single-agent immunotherapy, combination therapy would appear to be the most likely scenario to combat cancer. Future combinations will focus on complementary mechanisms of action, such as those that inhibit the checkpoint blockade and those that stimulate production of cytotoxic T cells. Other new and emergent mechanisms of action may come into play as well. That said, this is such a new area of exploration, and there is much work to be done. Without more combination trial data on immunotherapy agents together with and without chemotherapy, we aren't at the point where it's clear what combination therapies should be considered — yet, it appears clear that combining multiple agents may be the best approach for patients right now.

ESSENTIAL COMPONENTS?

We are only now in the early stages of this emerging field of cancer immunotherapy, a field which will undoubtedly evolve substantially over time. In the current environment, I would envision that a viable combination for many forms of cancer would include a CTLA-4 or PD-1/L1 blocking antibody or multiple checkpoint inhibitors as well as a vaccine/adjuvant to promote a robust cytotoxic T cell response against that cancer. However, groups are working with approaches that don't utilize checkpoint inhibitors at all, and these approaches may emerge quite rapidly.

BACKBONE THERAPY?

It depends on the setting. In the short term, checkpoint approaches will indeed remain an important part of cancer immunotherapy combinations for many, but not all cancers. One reason for this is simply that these checkpoint approaches were first out of the gate and will establish themselves as standard of care for a wide variety of cancers over the next few years. That being said, vaccine and costimulatory approaches will likely emerge as an equally important part of a combination regimen to combat cancer.

COMBO CRITERIA?

It is a complex and rapidly changing environment, and these are very expensive therapies. While physicians will, of course, be free to prescribe combinations as they see fit, regulatory, formulary, and reimbursement realities will certainly be an important factor in the care of most patients.

PERSONAL OR BROAD?

Both autologous and allogeneic approaches will likely have an important role in treating different forms of cancer. At Heat Biologics, we specialize in the development of a novel, fully allogeneic cell-based approach to activate a robust pan antigen T cell immune response against a patient's cancer. Our approach offers certain cost, convenience, and logistical advantages. However, other approaches, such as autologous CAR-T therapy, appear to offer a very promising approach to treating certain cancers as well. In short, I can see a role for both types of therapy in different settings.

Cell-based approaches may eventually become part of the standard of care for many types of cancers because of the many unique properties that they possess. Allogeneic cell-based approaches offer the best opportunity to overcome the cost and logistical constraints preventing dissemination of cell-based immunotherapies as a class. Allogeneic approaches do not require extraction of material from a patient or personalized processing and are therefore much more cost-effective. There are fewer logistical or timing restraints, and patients may begin therapy immediately.

COMMERCIALIZATION CHALLENGES?

Modern immunotherapies are still relatively young. We know that immunotherapy does not behave the same way that traditional cytotoxic chemotherapy

does in terms of dose response, safety profile, and lag time to efficacy, and many of these parameters are still being evaluated in the context of clinical trial design.

In addition, while the U.S. FDA currently does not regulate cost-effectiveness of medicines, there is a clear need from a consumer and payer perspective to consider the value of products; therefore, the high cost of developing biologic products requires thoughtful streamlining of drug development processes and consideration of reimbursement strategies early on in the drug-development process.

GENERAL COMMENT?

Immunotherapy is an emerging and rapidly changing area, and it is difficult to predict which approach or combination will be effective for a given cancer type. Given the promise of immunotherapy to treat a wide variety of cancers, it is important that we explore not only appropriate combinations, but also the issue of cost-effectively delivering these combinations to patients who need them.

ONCOSEC MEDICAL

Developing intratumoral electroporation of a plasmid DNA construct encoding the Interleukin-12 (IL-12) protein to stimulate production of tumor-infiltrating lymphocytes (TILs) complementary to PD-1 inhibition.

ROBERT H. PIERCE, M.D.,
Chief Scientific Officer
(Former member of the global development team for the anti-PD-1 program [pembrolizumab] at Merck & Co.)

WHY COMBINATIONS?

Our drug-development strategy is to combine our IL-12 treatment with anti-PD-1 or other checkpoint inhibitors because the two mechanisms seem to work together so well. There is a "monotherapeutic fetishism" in traditional oncology; many good drugs probably would be extremely safe and have synergistic activity when combined, but they never get through development because they don't show monotherapy activity. Fortunately, intratumoral IL-12 electroporation has monotherapy activity. So, how do we augment the immunogenicity of tumors? We use intratumoral electroporation to deliver IL-12, which sits at the top of a hierarchy of cytokines, which drives immunogenicity and potent antitumor immunity. This is not just a local ablation. With the intratumoral injection of IL-12, we get systemic immune responses in more than half of the treated patients, and we are also getting a large TIL response — the key to boosting response to anti-PD-1.

ESSENTIAL COMPONENTS?

All the possible components will have to go through clinical trials. The entire clinical and regulatory community recognizes that the future will bring more combination immunotherapy trials. We need to figure out means to choose rational and safe combinations and make the process more practical. Even when you have squeaky-clean molecules, regulators understandably worry about synergistic toxicities. Anti-PD-1 has a really low toxicity profile compared to say, ipilimumab or IL-2, and with our IL-12, we haven't had a single drug-related serious adverse event. But it's fair to say, if you're having synergistic efficacy, you may also have synergistic side effects.

BACKBONE THERAPY?

PD-1 therapy is a straightforward story: If you look in a microscope and you see the PD-1+ TILs in the tumor nestled together with PD-L1+ tumor and macrophages, that patient will likely respond to an anti-PD-1 drug. That is a beautiful piece of biology, but the vast majority of patients do not respond to anti-PD-1 monotherapy. This is the biggest unmet medical need in immunotherapy.

NARROW OR WIDE APPLICATIONS?

While I was at Merck, we developed an anti-PD-L1 antibody immunohistochemistry assay, and it became immediately clear that — across the board — there exists a subpopulation of patients in most all tumor types who have the PD-L1/PD-1+ TIL "adaptive resistance" phenotype, which

we know predicts response to PD-1 or PD-L1 therapy. So, the potential benefit of checkpoint inhibition cuts across almost all cancers. We have to think of tumors in a new way. In looking at response to immune checkpoint therapy, the tumor's tissue and cell of origin doesn't seem to matter as much as the immunophenotype. In particular, this means the presence of the right TIL signature.

PERSONAL OR BROAD?

It is not wrong to think of our IL-12 drug as in-situ vaccination. But unlike other vaccines, in delivering IL-12 into the tumor, we don't have to rationally choose a specific antigen to suit the immune system in a particular patient. Some of the more forward-thinking vaccine technology engineers a synthetic consensus of multiple antigens. We solve the problem by killing tumor cells in situ, releasing all the potential antigens present in the tumor, and letting the immune system sort out what antigens are important for response.

COMMERCIALIZATION CHALLENGES?

We are already in discussions about a combination of anti-PD-1 and our drug, and there are a lot of other immunotherapy companies thinking along the same lines. Novel-novel combos are particularly challenging from a regulatory perspective. We have already seen examples of enhanced toxicity with combinations of immunotherapies. And we certainly don't have predictive models for these therapies. Intratumoral gene therapies like ours present a preclinical safety assessment challenge because the mouse tumor models are of such short duration, typically less than three to four weeks. As a community, we will have to work toward better solutions.

We have another unique challenge: IL-12 has been shown to convert myeloid-derived suppressor cells into real APCs (antigen-presenting cells). We are in effect (not actuality) converting a tumor into a lymph node, so we don't want to kill off the tumor completely too fast. We need to apply just the right amount of IL-12, because we need the conversion to take place and leverage the local effects to drive a systemic antitumor response.

THE MODERATOR CLOSES

Roundtable moderator Llew Keltner draws some basic findings, lessons, and urgent challenges from the entire discussion in bringing this five-part series to a close.

KOLs & COMPANIES IN COMPARISON

One of the chief aims of this virtual roundtable was to see how closely the views of key opinion leaders and company leaders matched — either among the peers in each group or between the two groups. One fact we discovered immediately was the extensive overlap of KOLs and companies in the cancer immunotherapy field. It is as if the intense excitement generated by the unprecedented responses in human trials drove key academic researchers to work with industry as never before to see the new agents all the way through to marketing approval.

Nevertheless, the KOL community also hosts the most-guarded, even pessimistic views of immuno-oncology, just as companies are the source of greatest optimism — unless, of course, they are speaking of a rival approach. (See "Companies — Convergence & Divergence.")

We found a nearly uniform consensus on every side of the discussion that cancer immunotherapy is now a commercial and clinical reality, and combinations will be required for maximum clinical benefit. Some notable exceptions exist, however, including the belief, as expressed by KOL Alan Venook, that current data is insufficient to prove the case. (See Part One.)

We also saw a general admission that a great deal remains to be discovered about the mechanisms of action (MOAs) in the new immunotherapies, as well as MOA interactions in combination, the role of different immune-cell types, patient variability, and tumor variability in regard to immune response. But the scientific uncertainties will not deter aggressive development in the field.

IN THE GAME

An overall picture emerges: It has become difficult to be an "oncology company" of whatever size without an effort in immunotherapy. With the consensus that immuno-oncology will constitute 80 percent or more of oncology drug therapy in the relatively near term, companies — particularly public companies — that do not claim to have immunotherapy efforts are falling out of favor with investors. Almost every company without an immunotherapy compound is trying to get access to anti-PD-1/anti-PD-L1 for a trial. Even mid-cap oncology companies are driving very hard to get into the space.

Available assets in the cancer immunotherapy space for the big and midsize oncology companies are becoming extremely scarce. For example, there are many outdated, questionably effective cancer vaccines available, but almost none of them work alone or even in combination. The older agents have been far surpassed by a very few newer, more elegantly designed vaccines, which are already taken by the big players or aspirants. There are virtually no clinical-stage checkpoint inhibitors or costimulatory molecules available, and even the preclinical ones are being heavily pursued.

Thus, some companies appear to be grabbing at theories — small molecules or antibodies that affect one axis or another — that seem like a good idea in combination with real immune modulators. Some of those will indeed prove to be good combination molecules, but may have a hard time competing with lower-cost existing alternatives. For example, low-dose metronomic oral cyclophosphamide, which is essentially free, nontoxic, and easily acceptable to PIs and IRBs, has generated very striking data in combination with vaccines, checkpoint inhibitors, and costimulatory molecules.

The largest overlooked area among the immunotherapy companies is ablation. Despite huge support and demand from KOLs for apoptotic ablation modalities in combination with immunotherapy drugs, the big players have almost universally ignored the area. They have all also missed the huge intellectual property opportunity available to them in combining immunotherapy drugs with ablative modalities.

> "IT HAS BECOME DIFFICULT TO BE AN 'ONCOLOGY COMPANY' OF WHATEVER SIZE WITHOUT AN EFFORT IN IMMUNOTHERAPY."
>
> **LLEW KELTNER**
> Roundtable Moderator

The overhang of "targeted" drug development persists strongly in immunotherapy, particularly among the Big Pharmas. Virtually all of the big players are searching for "biomarkers" to select patients for trials or commercial use, despite the evidence that the most obvious biomarkers, such as PD-L1 expression in tumors, do not reliably predict response.

A huge misunderstanding of clinical reality persists in regard to immunotherapy biomarkers: With the targeted therapies, it is quite simple to look for a variant gene or target molecule in peripheral fluid, but in immunotherapy, virtually all of the proposed biomarkers are in tumor biopsy tissue. Arguably, tumor biopsies will simply prove commercially impractical; it is unlikely that patients, physicians, and payers will routinely tolerate them. Medical oncologists do not typically have the capability to do biopsies, which require referrals to interventional radiology for a dangerous, expensive, and often very uncomfortable procedure.

The importance of affordability and practicality came up numerous times in our roundtable discussion. But trouble has already appeared on the horizon. Though in a different area, Gilead's premium-pricing of its liver-disease drug Sovaldi (sofosbuvir) and its successor, Harvoni (ledipasvir and sofosbuvir), has created a tough and questionable future reimbursement environment for new combination cancer-immunotherapy drugs. The U.S. Congress is now talking about rolling back patents for drugs deemed essential but too expensive, and the U.S. Department of Veterans Affairs is looking at a number of mechanisms for reducing the cost of specialty drugs, including oncology. For example, at a recent Congressional hearing concerning Sovaldi at the VA, the concept of the federal government "walking in" to the Gilead Sovaldi patents was discussed. Payers, federal entities, and health economists are talking about value-based reimbursement — essentially paying for success only.

Characteristically, pharma companies are being sluggish about jumping into the debate and openly working with payers to negotiate pay-for-success schemes for cancer immunotherapy, even though, with potentially huge increases in patient benefit, there is a phenomenal opportunity for profit incrementation. Ultimately the payers will force the issue, so the financially successful immuno-oncology (IO) companies may well be the ones that quickly plan and execute clinical trials that provide pharmacoeconomic data to support value-based, success-based reimbursement.

GAME CHANGERS OR CHANGE GAMERS?

Meanwhile, immuno-oncology marches on. Virtually all of the large pharmas with oncology franchises are either developing IO drugs or are actively hunting for IO assets. Almost all small and midsize oncology companies have recast themselves as cancer immunotherapy developers or are struggling to get into trials with their nonimmunotherapy assets in combination with anti-PD-1/anti-PD-L1.

Unfortunately for the big companies, new clinical-stage IO assets among the currently exciting approaches are available for licensing. As a result, the group of companies actively hunting for assets — Merck, MedImmune, Sanofi, GSK, Novartis, Pfizer, Bayer, Boehringer Ingelheim, Roche, Daichi Sankyo, Medivation, Lilly, Abbvie, Takeda, and Kyowa Hakko Kirin — are now all looking at preclinical assets.

KOLs in a number of cancer indications express rapidly increasing frustration with the resistance and inaction of the large companies to start combination IO trials. Some of the world's most prominent KOLs have been repeatedly rebuffed by big pharmas that cite concerns about safety, intellectual property, GMP supply, "lack of clarity on approval pathway," and other rationales for inaction.

Thus, an already big gap between KOLs and companies in cancer immunotherapy may grow even wider as business, not scientific, issues create the greatest impediment to its development and adoption. Will Big Pharma miss another historic opportunity to champion a therapeutic revolution with cancer immuno-oncology? Can the small companies make up for pharma's inertia? Once again, as with all great endeavors, the real question is, will the optimists or the pessimists prevail? And this time, the whole world — particularly the cancer patients all of us in the industry must serve — really will be watching for the answer. L

THE COMPANIES — CONVERGENCE & DIVERGENCE

Like the KOLs, company leaders agreed on some issues and disagreed on others:

AGREEMENTS:

- IO will become dominant in cancer therapy in the relatively near future.
- IO agents will be primarily used in combination.
- Long way to go in understanding the underlying science
- Best combinations are not currently known.

NO AGREEMENT/CONSENSUS:

- Need for use of biomarkers in IO for patient selection
- Commercial feasibility of autologous cell vaccines
- PD-1/PD-L1 as a long-term backbone for IO
- Corporate methods for selecting, developing, and commercializing IO combinations
- Utility of using non-IO agents in combination with IO agents
- Strategies for working with partners who own the other drugs in specific IO combinations
- Universality of application of IO to all cancers
- Ease of obtaining reimbursement for IO combinations (pricing)

Salvaging Value In Divestitures

FRED OLDS Contributing Writer

The unfortunate truth is that most business divestitures are characterized by value destruction from inception to close. That's PwC's conclusion about divestitures according to Glenn Hunzinger, a partner at PwC Transaction Services. "Selling a business is probably the hardest thing a company can do," he says.

Business leaders underestimate the detailed planning required. Sellers often end up in front of a buyer unprepared to answer many of the buyer's questions, and the process begins to linger as the seller scrambles to answer those questions. The longer a divestiture takes to close, the greater the risk to the seller's value proposition.

Unless a company has participated in a divestiture previously, it's not uncommon to have the misconception that the effort will be quick and easy with leadership providing inadequate time and resources to the process. "People have day jobs. Divestiture is just what they do after 5 p.m., and it gets second-class attention," says Munzoor Shaikh, senior manager of healthcare transaction services at West Monroe Partners. Consultants such as Hunzinger and Shaikh say divestiture plans often lack a clear strategy and will present with an overly brief diligence that doesn't have an objective valuation or a clear definition of what's being sold, or include encumbrances that may be linked with the business or asset being sold.

WHY IT'S IMPORTANT TO ASK WHY

Hunzinger says that leaders should conduct regular reviews of their business and evaluate whether divisions meet the long- and medium-term visions for the company. It's at this point that divestiture becomes a consideration. "When opting for divestiture, the critical question to answer is the 'Why' of the strategy," says Shaikh. Answering this question affects the process. For instance, if the strategy is purely to generate cash to dedicate to the core business, the guiding principle may be speed. The guiding principle becomes risk, however, in a situation in which Company A is divesting itself of a subsidiary that happens to be a supplier of critical compounds. Shaikh says Company A might need to take more time to mediate risk and ensure there is no interruption of critical supplies during and following the divestiture.

CONSIDER THE TYPE OF DIVESTITURE

When a company chooses divestiture, says Hunzinger, it has to answer two questions: What does the end business look like? What is the right process to achieve that end point? Consideration has to be given then to the type of divestiture. "Selling to a large corporate entity is a lot easier than selling to private equity or creating a spinoff," says Hunzinger.

Spinoffs, he says, leave no slack time for acculturation; they have to be up and competitive on day one. Creating the right culture and structure are critical. Leadership needs to look at the market to analyze the competitive environment and corporate structure that succeeds there.

Using this knowledge, the mother company has to structure the spinoff to compete in that market. Hunzinger says, "Often leadership just mimics the structure of the parent company. There has to be a more strategic view." After all, the needs of a small biotech or device company are very different from those of a large multinational.

Divesting to private equity carries many of the same considerations because equity companies usually don't have the infrastructure to support a new business. The seller may have to provide some support systems until equity can contract or hire resources to fulfill those needs. The nature of the resources, the duration they will be provided, and the expense need to be fully detailed in the contract.

PREPARE THE BUSINESS TO BE SOLD BEFORE YOU OFFER IT FOR SALE

"You cannot plan enough," says Hunzinger, "Up front, set a defined perimeter regarding the transaction object [what's being sold], have all the data, and complete a detailed diligence. The more you do on the front end, the faster the back end goes."

Divesting a business unit or asset requires a high degree of detailed oversight and planning. "Even something as seemingly simple as wanting a file from the regulatory system can be complicated," says Shaikh. Proprietary information can be hidden in documents, emails, and various programs. All of these have to be reviewed and vetted by the people or business units responsible for their generation.

Too often companies fail to leverage the positives or address troublesome issues associated with the business. Leadership has to provide supporting evidence of the positives. "And you must be prepared from the outset to put all of the issues — good and bad — on the table," says Hunzinger. "Then you will be able to tell the buyer what you are doing to address them."

"The more you prepare up front, the more you understand the business," says Hunzinger. "This preparation will provide the data to construct a well-designed sale offer and will enable you to handle any situation during the sales process."

THE KNOWN, THE UNKNOWNS, AND THE UNKNOWN UNKNOWNS

"In a divestiture there are the 'knowns', 'unknowns', and 'unknown unknowns,'" says Shaikh, "and you have to prepare for all of them. In other words, expect the unexpected." He explains that a common "known" is that an inventory system will have to be converted from Company A to Company B. This is handled routinely. Or, perhaps, Company A's quality program needs to be implemented at Company B. But how these conversions and implementations are conducted is an example of an "unknown." Planners need to estimate the time and steps necessary to align the programs and allocate that time into the divestiture plan.

In every project, however, situations arise that are completely unanticipated ("unknown unknowns"). Shaikh says you have to schedule time into the divestiture plan to account for these situations. IT debt is a common occurrence. Companies buy customizable ERPs (enterprise resource planning) to manage business processes. The more customized they become, the more difficult the divestiture. Over time, layers of customized technology are applied to one another. Artifacts and unauthorized workarounds from previous editions may remain and cause dissonance in expected outcomes.

For instance, a company may say its average market price (AMP) is computed in the I-many program. Yet AMP printouts don't match expectations, because seven years ago a portion of the AMP computations was switched to the finance system. Untangling these situations becomes an exercise in forensics. These irregularities in IT can compound over time and be difficult to untangle.

THE PROCESS

Hunzinger says a company must allocate resources designated specifically to guide the divestiture. This includes oversight and direction from a leader appointed to drive the project. A dedicated unit/section should be created, composed of interdisciplinary teams representing all of the functional divisions of the company. These teams must understand how their work relates to that of others and how all of them relate to the divestiture.

IT and the business units must all work together throughout the process, says Shaikh. Tech is the foundation of communication in most enterprises. It is the sinew that links the parent company to the business units. Slicing off a unit or product will require some restructuring of the enterprise, the unit, and the IT system.

BE OBJECTIVE WITH YOUR VALUATION

Company leadership is often too close to the business unit to have an objective understanding of its value. Leaders need to look at the unit through the eyes of a buyer.

"Often leadership is looking at its business and product lines without all of the associated costs/expenses. So, the offer doesn't have a measure of true profitability," says Hunzinger. "That leads to a disconnect between the seller's perception and what an outside party perceives the value to be." Examples of these oversights include pension obligations, tax exposures, indemnifications, and debt.

There are other expenses that may detract from the value of the sale. A buyer may ask to subtract the costs they will incur to provide infrastructure and support to the new division business. Sellers may find they are left with personnel or systems that are no longer needed, now that the divestiture has been completed. Associated transaction expenses such as lawyer fees, filings, consultant fees, and banker fees should be considered in the value proposition.

> *"You must be prepared from the outset to put all of the issues — good and bad — on the table."*
>
> **GLENN HUNZINGER**
> Partner, PwC Transaction Services

To substantiate the potential profitability of a company, sellers must convince buyers that their forecasting methodology is reliable. In today's business climate, it may be difficult to convince a buyer that historical forecasting is a good prediction of future revenue production. Sellers must develop and validate models that produce convincing results.

AVOID AMBIGUITIES

An offer to sell has to be explicit. Shaikh says, "An offer might say, 'The seller retains no right to the existing assets, and the buyer gains all rights to the existing assets.' The question then becomes what are the existing assets?"

It's very difficult to conclude a divestiture if, during the process, the seller is ambiguous on what's being sold. "Defining a transaction object is one of the biggest places companies fall short. They don't set parameters up front," says Hunzinger. Sellers sometimes add or retract assets, personnel, or entities to or from the sale during negotiations. This muddles the sale and extends the process.

A primary goal in divesting has to be the reduction of ambiguity. The seller should present an offer that leaves few questions and increases confidence on the buyer side. That speeds the sale and salvages value. L

From Publish-Or-Perish To Product Creation – Putting Your Research Into Action

CHIP REUBEN Contributing Editor

Neoantigenics is a biotechnology company that was based on unique IP that was discovered at the University of Virginia (UVA). John Herr, Ph.D., chief scientific officer, is the principal investigator and a tenured professor in the Departments of Cell Biology and Biomedical Engineering at UVA.

He is widely known as a world-class reproductive biologist who discovered that proteins, normally unique to the growing egg (as opposed to the ovarian reserve or later stages, such as after the formation of germ layers), were also showing up in cancers, making them viable and specific targets for cancer therapeutics. Dr. Herr had previous experience starting a company, but he couldn't do it alone, so UVA insisted he get help from Brian Pollok, Ph.D. Pollok, CEO of Neoantigenics, is a talented entrepreneur with roots at UVA. He has ample previous experience with both Pfizer and Life Technologies (currently owned by Thermo Fisher). The executive team of this new venture was further strengthened by the addition of Ed Leary, CFO, who had previous experience starting a diagnostics company with Dr. Herr. Leary came in with an understanding of how to raise funding for a new company without diluting its future value. It was the formation of this trio dream team of complementary talents that was pivotal in the rise of Neoantigenics from within the university.

WHAT TO LOOK FOR IN A NEW BIOTECHNOLOGY COMPANY

"The most important item is to create high value intellectual properties that are owned by the institution," says Dr. Herr, who had been working since 1995 on developing an oocyte proteome and publishing his results. That work provided him with the insight that some of these proteins were showing up in cancer as neoantigens. So he identified cell models that expressed a candidate target, and he created prototype immunotoxins and showed that you could kill cancer cells via this class of target. By 2008 there were seven disclosures and two patent families. "There was a firm patent foundation on which to build," says Dr. Herr. Patents were based on the demonstration that the SAS1B neoantigen had membrane forms, that it had high incidences in many types of cancers, and that it could be targeted by immunotoxin drugs to kill cancer cells. Because the target was restricted to oogenesis and growing eggs, you could come up with a way to selectively target cancers. This is the most important observation. All of those insights are packaged into the IP pertaining to "cancer oocyte neoantigens." These antigens are showing up in a wide range of tumors, including pancreatic, breast, head and neck, ovarian, and uterine cancers.

Pollok, who is entrepreneur-in-residence (EIR) at UVA, emphasized the key items required to get the company started. "Before negotiating a license, the university insisted there be a team of complementary talents. They wanted somebody to work with Dr. Herr who could not only understand the science, but who also had firsthand experience at biotechnology or pharmaceutical companies and understood how to effectively raise money." After the A team trio formed, the licensing negotiations began and took only four months to complete. "Relative to other processes I've dealt with, it wasn't a long time," Pollok says. The university has continued to support the company through access to facilities, contacts, a network of advisors, venture firms, and pharmaceutical companies for advice. "I feel very much a partner with UVA through my CEO role at Neoantigenics," he adds.

For investors of companies like Neoantigenics, a small amount of

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capital (i.e., several hundred thousand dollars) can pay large dividends. Neoantigenics essentially runs in virtual mode with no brick-and-mortar. The lab space is all at UVA or at third-party contract labs. Pollok has an office at UVA as part of his EIR role. "The company executes its work either through the university or through third-party contractors," he explains. He also emphasized the value in looking for unique science (i.e., not "me too" companies) and for partners who will be transparent and not "hold you at arm's length."

WHAT WORKS AND WHAT DOES NOT

Once Neoantigenics had its core team together, it was able to go from term sheet to signed license in four months because the university was realistic about the financial terms it was willing to accept. The university was looking for a payback from the investment in the intellectual property, but it wasn't looking to soak the new company. In fact, a lot of the up-front expenses were waived. The university didn't take a huge chunk of the company in terms of equity; it has a single-digit minority stake. According to Leary, requests for ridiculous royalty rates strongly limit an ability to partner with someone down the line because whoever acquires this technology would carry this royalty obligation to the university.

Neoantigenics has a research agreement with UVA that enables Dr. Herr's lab to continue the science on which he's been working. UVA also stood to gain from the intellectual wherewithal of the entrepreneur, acknowledging the need for conflict-of-interest management. According to Michael Straightiff, managing director, UVA Innovation, Pollok's appointment as EIR was to UVA proper rather than to Straightiff's 501(c)3 organization within UVA.

One of the roadblocks to finding early funding was a lack of definition of what the drug candidate should be. The ones who were willing to step in initially were the local angel investors and state-supported funding agencies. Substantial support came from the Center of Innovative Technology (CIT), Virginia Biosciences Healthcare Research Corporation, and the Wallace H. Coulter Foundation. "A total of 60 percent of our seed funding has been nondilutive funding," explains Leary (nondilutive capital is that which does not affect the ownership of the company).

"The company executes its work either through the university or through third-party contractors."

BRIAN POLLOK, PH.D.
CEO, Neoantigenics

The initial crafting of the Pfizer deal was focused on the science first and the business second. When Neoantigenics presented to Pfizer initially, they were so interested in the science that they wanted to license the technology outright. Ultimately, however, Neoantigenics decided that they could make the antibody scaffolds themselves. They would raise money, reach out to angel investors, and partner with the best technologies in the world. Using this support, they planned to subcontract research and partner with people with optimal drug payloads. The big partner, Pfizer, remained very interested in the target, and after the company decided to create a start-up, Pfizer decided it also wanted to offer seed funding to the company. Neoantigenics holds extremely valuable working group sessions with Pfizer during which they obtain technical advisement. The arrangement with Pfizer has provided significant in-kind value to Neoantigenics, helping them to raise a total of $2 million (including other funding sources).

THE BALANCE: OPTIMIZING THE BUSINESS AND UNIVERSITY INTERESTS AND INTERRELATIONS

Pollok emphasized the need for a balance in decision making between the company and university, and the need for separation of responsibilities of corporate and university employees. The interrelationship can be synergistic, but checks and balances are important. For example, the entrepreneur should take primary responsibility for any fundraising that requires offering shares, whereas the principal investigator should handle the nondilutive funding that flows through the university. The entrepreneur also should create and manage the budgets in the company. If individuals at the university are left to R&D without oversight, the company won't get what it needs. Similarly, the company should not be able to go off to do its own thing without some tie-in and critique from the university inventor, who should have oversight of any university staff who are working on the project.

It is important to note that Ph.D. students and postdoctoral fellows are looking to get published for their work for Neoantigenics, which is encouraged by the company. But there has to be a balance between meeting the corporate development goals and the publication goals of the university trainees. An example might be a student wanting to find something novel by spending extra time on a specific project that the company hasn't directed. Neoantigenics doesn't want to discourage such research, but it also needs to manage what is contracted with UVA. Furthermore, there is an economic impetus for scholastic research to align with corporate goals as less money becomes available from NIH for the basic research. "To keep these labs doing their research, I think more of this money is going to come from industry," according to Leary. "Our relationship is with John Herr. He has the obligation with his students to publish and find novel science, but also to meet the goals of the industry research agreement that is funding his lab."

Leary discussed one very important business optimization question about when to shift the emphasis over to the expertise of Big Pharma. Early on, Pfizer wanted to license the target outright. In that case, it would have set up a research agreement with UVA to get the basic science done. The research would have continued to be done at UVA until it

was time to migrate the research out of the university to the pharma company, which would then add its expertise. But Neoantigenics and UVA had more value to gain by taking the science further than it was when Pfizer wanted to license it, acknowledging the risk is the expense. The cost has been ~$1.1 million since the point that Pfizer wanted to license it. So the university has to ask whether the start-up has the management team and the capability to raise the money through grant funding or investment in the company, or are they just going to stall or fizzle out and end up licensing the technology to pharma anyway. It's the university's role to make this decision. If the start-up can advance the technology, then there is a greater return for the university because it would end up with a higher royalty rate than it would have had there not been as much science proven as there is now.

Dr. Herr has expertise in reproductive biology, characterizing the targets and creating antibodies to those targets. But ultimately the company will need a partner that has expertise in combining or conjugating those antibodies to various effectors such as antibody-drug conjugates (ADCs), chimeric antigen receptors (CARs, artificial T cell receptors are under investigation as a therapy for cancer), or vaccines. Typically, this kind of partner would be a pharmaceutical company. This could be done with Pfizer, but it doesn't necessarily have to be Pfizer. According to Pollok, "The most likely path is that we develop the IP to the point where we de-risk the target biology for the pharmaceutical company partner." Neoantigenics is well on its way to fulfilling what it had projected to accomplish, which was to raise $2 million and then have the antibody to a specific cancer target by end of 2014.

"A total of 60 percent of our seed funding has been nondilutive funding."

ED LEARY
CFO, Neoantigenics

According to Straightiff, UVA hopes for rapid progress in the partnership of Neoantigenics with the pharma experts for later-stage therapeutic development. "With Neoantigenics we were very fortunate that a very compelling strategic partnership evolved almost immediately. That gives us a great amount of confidence. L

Quality Agreements In Clinical Development: A Road Map Toward A Successful Partnership

JONATHAN LEE AND MARY CHOW

With clinical research continuing the trend of outsourcing more clinical trial activities to clinical service providers such as CROs or other vendors, it has become critical for sponsors to ensure that the activities they have outsourced are performed in accordance with the sponsor's quality expectations. Because of shortened development timelines, often after a rigorous selection process, the clinical service provider immediately starts work on the project without the benefit of both parties discussing their expectations of quality.

Based on the data collected in a 2011 Avoca Industry Survey of sponsor organizations, only about 65 percent of respondents had written quality agreements with their CROs. However, in the same survey, 94 percent of the respondents that used a quality agreement were satisfied with their CRO's performance, while only 59 percent of the respondents that did not use a quality agreement were satisfied with their CRO's performance. This supports the idea that establishing a quality agreement is crucial in building a strong relationship between sponsor and CRO.

ESTABLISHING A QUALITY AGREEMENT

Quality agreements are well-established in other industries such as manufacturing and finance; however, such agreements are just starting to be applied to the conduct of clinical studies. A number of sponsor companies are participating in various consortiums such as the Avoca Quality Consortium, which developed a standard quality agreement template with metrics. Some examples of these metrics, or Key Quality Indicators (KQIs), are turnover rate for key personnel, commitments to holding quarterly risk management meetings, number of corrective and preventive actions (CAPAs) implemented, and CAPAs resolved within the time frame specified in the CAPA.

The quality agreement provides an avenue and structure to set the expectations of the parties, identify any deviations from these expectations, and specify an escalation process to address/mitigate these deviations. The key to successfully negotiating the quality agreement is clear communication of expectations between the parties and the emphasis on each party having a sense of ownership over the study through mutually created, agreed-upon language.

HAVING THE CONVERSATION

We found that when introducing the quality agreement and associated metrics to our company, we first needed to evaluate as a team how it fit into our overall clinical service provider governance model. This led to discussions of our company's expectation of quality, which was followed by significant negotiations regarding the proposed metrics. Briefly, our company's clinical service provider governance model is centered upon a master service agreement (MSA) with each specific study's scope of work described in an addendum. The quality agreement is executed as a separate contract which leverages the MSA, and it details expectations of quality with associated metrics for all projects outsourced to the specific clinical service provider. The metrics contained within the quality agreement represent items agreed-upon as indicators of quality aggregated across all of the outsourced studies. Each MSA addendum that describes each individual study has a service level agreement (SLA) that contains agreed-upon expected service level, penalty, and bonus language for that particular study.

We found our quality agreement discussions to be an enlightening process, which created dialogue with our vendors and CROs, building more meaningful relationships among the parties. For example, one metric in our quality agreement required the reporting of all critical audit findings from regulatory authorities or sponsors within a contracted region regarding a contracted service. The specific clinical service provider's QA representative stated that they were unable to agree to this metric due to their obligation to maintain confidentiality of their clients. This led to a discussion about the root of the metric, which was to provide assuredness that a robust process is followed when assessing the potential impact of critical audit findings upon other programs within the region or other programs which use the same service. We explained to the QA rep what we would expect of a robust process, and the clinical service provider reassured us that they had SOPs and work practices (WPs) which governed the assessment of potential impact upon other programs. However, while the essence of what we described was detailed within their SOPs & WPs, the QA representative agreed that their process could be enhanced to meet our expectations. This led to a revision of their SOPs and WPs.

Another example of how our quality agreement negotiations facilitated collaboration was our discussion with a CRO around the commitment to have, at a minimum, a quarterly risk management meeting to identify risks and set up mitigation plans. In this discussion, we were able to introduce the CRO to the usage of the failure mode and effects analysis (FMEA) tool in risk management for our studies. Both parties committed to setting up a process to manage risk in the quality agreement, where the specific details were to be discussed in future meetings.

Two common objections raised by vendors during the negotiations of the metrics included how sponsors perceived that the required resources to collect and manage the metrics may deter from vendor's actual performance of their study-related tasks and how certain metrics may be impacted by forces outside of vendor's control. In the first instance, we made an effort when negotiating the metrics to continually assess what metrics the clinical service provider typically collects, therefore only pursuing additional metrics if we felt it was absolutely necessary. When considering the metrics which may be influenced by forces beyond a vendor's direct control, we were careful to allow "carve outs," which included "acts of god," natural catastrophes, and unforeseen regulatory authority changes. Aside from these common objections, both parties acknowledged that the goal of the quality agreement metrics is to help assess whether or not there is a pattern across all of our studies that can be learned from and applied to ongoing and new studies, in order to avoid a repeat of common sponsor/vendor grievances.

CREATING A WIN-WIN SITUATION

Critical to negotiation success and implementation of the quality agreement and metrics was the participation of senior management from each company and their respective clinical and quality teams. This was important because it identified what each party thought was important in conducting a quality trial.

The collaborative approach of establishing a quality agreement creates a sense of ownership of the project by all parties involved, with the common goal of conducting a quality study. This will ensure a "win-win" situation where both parties are committed to meeting their responsibilities without finger pointing and the focusing of one-way faults on the vendor for not meeting sponsor standards. As a result of the implementation of a quality agreement, a sponsor has a study that meets its expectations, and the vendor has gained the trust of the sponsor, hopefully leading to more successful future collaborations. L

Jonathan Lee is VP of development operations at Cerexa.

Mary Chow is director of contracts management at Cerexa.

Janssen Pharmaceuticals R&D Adopts A Venture Capital Innovation Model

FRED OLDS Contributing Editor

Faced with diminishing returns on R&D investments, large pharmaceutical companies are searching for innovative ways to successfully identify, develop, and market products with financial viability. Yet small discovery companies and biotechs continue to outpace large pharma in the approval of NMEs (new molecular entities).

These smaller companies seem more able to adapt and adopt new technologies nimbly to meet changing landscapes. Janssen Pharmaceuticals is meeting the challenge by adopting a small venture discovery model, the Janssen Incubator (JI).

Every year scientists in Janssen's R&D department make discoveries outside Janssen's areas of focus. While Janssen recognized the potential of many of these discoveries, it also recognized two obstacles. First, developing these findings would draw resources from current projects, and second, Janssen did not have expertise in these research spaces. In 2010, instead of selling the discoveries, the company decided to allocate a slice of R&D resources to develop a system to select the most-promising targets for further research. The result was a model that had focus, speed, and economy. This was the genesis of the JI.

THE RATIONALE FOR THE INCUBATOR

Sanjay Mistry, Ph.D., head of business operations at the JI and lead of natural product discovery, says, "The JI is an operational model which ensures we do not leave high-value assets on the shelf." He says it's an opportunistic approach to create value in science outside of Janssen's current focus areas. The endpoint of a JI project might be the starting point for NME pipeline development internally. It could also become a start-up, a joint venture, or some other entity externally.

"At its simplest level, the JI is an entrepreneurial approach to internal innovation," says Rob Willenbucher, M.D., head of JI and head of Janssen cell therapy. "It's a way for us to fulfill the Janssen mission of transformational medical innovation."

The model is very similar to that found in small venture capital R&D projects. Janssen forms small teams and gives them the resources necessary to meet milestones along the research trajectory. Both the teams and the resources are what Janssen refers to as "ring fenced." That is, they are dedicated solely to the project. Willenbucher says among the lessons learned is, "The teams can't be split amongst other priorities, and the teams need to know that the allocated financial investment is there for them."

Projects are selected annually. RFPs are solicited from scientists within Janssen for promising research projects outside of Janssen's areas of focus. The selection of proposals is based on a number of factors. For example, leadership looks at the underlying science, the addressable unmet medical need, the ability to identify milestones that have clear association with value creation, reasonable feasibility for success, or whether the project would benefit from the JI model.

During the selection process, there are cases where the science looks very good but feasibility may be low. In one case this year, two scientists came forward with very innovative science, but it was so early that it was hard not only to develop a business plan, but even to define a starting point. In cases like this, the board tries to find a home internally to provide funding to develop the science more fully. When that happens, the plan is to present those projects to the JI again.

The JI leadership knows that scientists most likely do not understand the business or financial aspects of a venture project. So after the first cut through the RFPs, a group of project leaders are selected to attend Janssen's Entrepreneurial Boot Camp. It is an eight-week educational program to

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»Mary Thistle, SVP, Business Development, Cubist

»Jack Tupman, VP, Corporate Business Development, Eli Lilly

teach a research scientist team leader how to think like a venture capitalist.

Business school professors from the U.S. and Belgium conduct didactic classes and facilitate projects. During the course work, teams develop business plans that include milestones and projected financing requirements. Willenbucher emphasizes the need to identify well-understood criteria from the beginning. "Milestones like start and stop dates and anything related to financing have to be clearly defined. The exit has to be explicitly described from the beginning. From the very start, the team has to understand and execute on the goal of achieving the next round of funding."

During the course, team leaders create and refine "pitch decks," which they present to the JI board of directors so the directors can conduct due diligence and make informed decisions. "From a business point of view, we want to make sure that, at the end, these projects can stand on their own and meet future market demands," says Willenbucher.

Currently the incubator has six ventures. Mistry leads a venture based on natural product discovery. There is a venture for autism. A team focusing on lupus is working on two projects, and there is a group researching a novel platform using a nonopioid pain product. A venture team is developing a multivalent biological targeting MRSA, and a team is creating a tool to facilitate the development of drugs that target G protein-coupled receptors.

PROCESS

Ventures are given a period of two to four years to meet milestones and reach their end points. Speed and economy of resources become the guiding principles. The JI places few restrictions on how team leaders reach their milestones. "The scientists get financial support, but they're expected to run the projects like any business," says Willenbucher.

Since these projects focus on science which might be outside the expertise of Janssen R&D, a venture may outsource activities. This provides economy by reducing the internal footprint of the venture. It can also speed results, by going directly to an entity that has needed expertise rather than waiting to develop it internally. "Anything and everything that you could potentially do inside, you might do outside," says Willenbucher.

Team leaders can and are likely to seek partnerships to support their research activities either internally or externally. "As an example of an external partnership," says Mistry, "one of our ventures is developing a clinical behavioral tool to better understand autism patients and how drugs may impact those patients. There are organizations like Autism Speaks which are very involved with that team. It's a broad opportunity for both the team and for Autism Speaks."

In the case of lupus — another science outside the company's area of focus — Janssen may not have the infrastructure to fully develop a compound. The company would be open to creating a joint venture with an enterprise that did have the expertise and resources. "In other research like early discovery programs such as natural product drug discovery, we're trying to move promising early-stage discoveries toward lead or NME status. Here, Janssen might partner with external entities to acquire financial support rather than create a full joint venture," says Mistry.

KEEPING PROJECTS ON TRACK, MEASURING SUCCESS

"Governance is a key aspect of this model," says Mistry. "Each of these ventures has a board of directors that the leaders report to once a quarter." During these meetings team leaders present progress reports on their research and discuss plans for reaching their next milestones. The board reviews progress, provides feedback, and offers opinions to the leadership.

The Incubator itself has a board of directors composed of leadership from within the organization. The JI board of directors makes decisions about overall portfolio selection and current portfolio operations. Mistry says, "They answer questions like, 'Should a project receive continued financing? Should a project be accelerated toward an exit? Is a project doing so exceedingly well that Janssen can capitalize on it now?'"

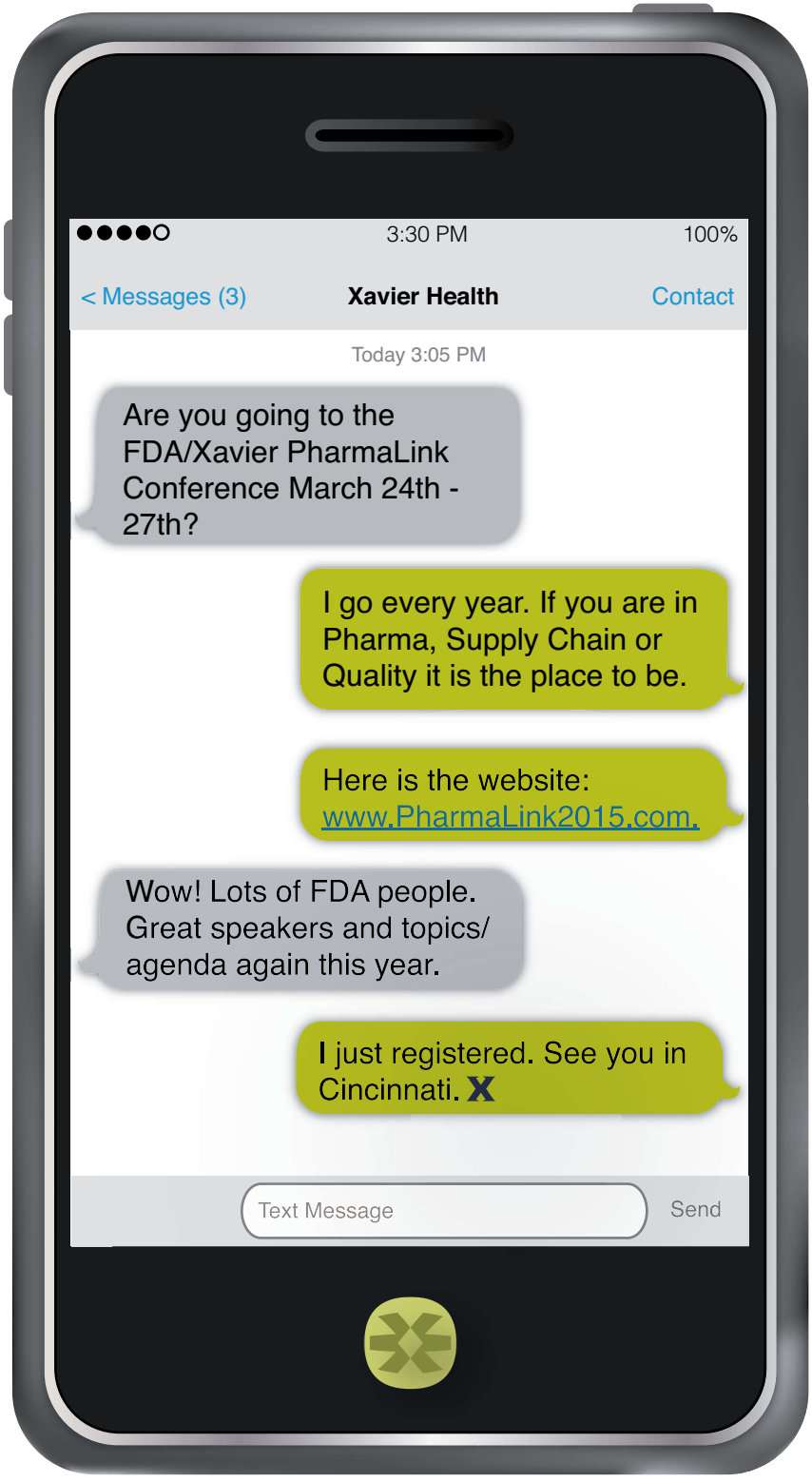
Governance ensures that a venture doesn't get off its planned course. Mistry says ventures are created like a start-up so it's critical they stay focused on their research and the milestones. "We're very rigorous in reviewing the financial and scientific decisions teams make to advance a program through its milestones," says Mistry. "If there are challenges, the venture has to decide whether it is investing its resources correctly or whether this research is fruitless."

"We judge success on the ability of our team leadership to meet milestones and garner additional financing either from within the company, from external sources, or a combination of both," says Willenbucher. Although none of the projects has yet entered clinical trials, in some cases they've entered into preclinical development to do IND (investigational new drug)-enabling work. One of the lupus assets has been taken into product development, and the team is in some initial discussions with potential strategic partners.

ADVICE AND LESSONS LEARNED

"The essence of entrepreneurship is the creative use of resources," says Willenbucher. Biotechs and small research ventures have been successful in the discovery of NMEs with limited resources. He says the incubator model adopts the advantages of that entrepreneurial model while providing the breadth and expertise of a large R&D organization.

Willenbucher says the model is the vehicle, but the most important thing is finding scientists who are passionate about their project. Not every scientist or discovery is suited for this model. "Leaders operating under funding and time constraints will find the fastest and best ways to reach value inflection points," says Willenbucher. "The totality of the experience is that it drives the engagement of team leaders, and because of that, projects move very quickly. That's good news for innovation."



FDA AND XAVIER HEALTH

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Overlooking GMP Biopharm Education/Training Can Cost You – Big Time

ALAIN PRALONG

Today, GMP-compliant manufacturing of biopharmaceutical drugs and vaccines is still only partially automated and not at the level of other manufacturing industries. Critical process steps such as sampling, sterile connection, or column packing are carried out manually by operators, which can negatively impact process reproducibility, product quality, and — in the worst case — even patient safety.

To mitigate risk and achieve compliance, extensive quality management systems (QMSs), including personnel education and training, have been built based on SOPs. Review of recent FDA enforcement actions (e.g., warning letters issued on 7/18/13 to Wockhardt Limited and on 8/9/11 to Beckman Coulter, Inc.) raises serious doubts about the efficacy of the current approach toward quality management and associated knowledge transfer methodologies. The FDA's findings indicate that personnel education/training, a lack of written procedures, and not following written procedures were among the top reasons priming enforcement actions.

Settlement of warning letters normally comes at very high cost. For example, Wockhardt executives mentioned that the cost of a warning letter could reach $100 million. Correction and control of this major quality risk exposure requires biopharmaceutical companies to adopt alternative approaches for integration of operator education and on-the-job training (OJT) with comprehensive quality management systems.

THE BIOPHARM INDUSTRY IS BEHIND

Greek philosopher Socrates spent significant time developing an education and training method for his students based on stimulation of the individual's power of reasoning. Since then, various other researchers (e.g., Ivan Pavlov, Hermann Ebbinghaus, Edward Thorndike) have strived to improve upon the process of efficient knowledge transfer. Interestingly, though, the biopharmaceutical industry has rarely adopted the concepts developed by these researchers and philosophers. Instead, highly educated process engineers and scientists have written comprehensive SOPs and batch records in an attempt to capture in wording all instructions and handling necessary for the execution of practical activities. Then, on the shop floor, operators with less scientific, GMP, and engineering understanding face the challenge of back-translating these instructions from words into practical execution of activities. This situation is prone to errors. Person-to-person understanding or interpretation of wording can vary and lead to issues with compliance since reproducibility is not ascertained. This situation is further aggravated by the widespread practice of operators not routinely consulting SOPs when executing tasks.

In the most modern stainless-steel-based biopharmaceutical manufacturing facilities, some of these problems have been addressed using process automation where applicable. Facilities are operated with sophisticated electronic building management and batch record systems (BMS and e-Batch Record) that improve process control and reproducibility by preventing operator errors. These complex systems come, however, at significant cost ($400 million+) and are most efficient in large-scale routine manufacturing. Interestingly, knowledge transfer to personnel is still based on SOPs, and a further negative consequence of this automation approach is that operators may lose track of process rationales and detailed understanding of executed activities. This exposes biopharmaceutical companies to significant risk of GMP noncompliance and process inconsistencies as a consequence of a "push-the-button" approach.

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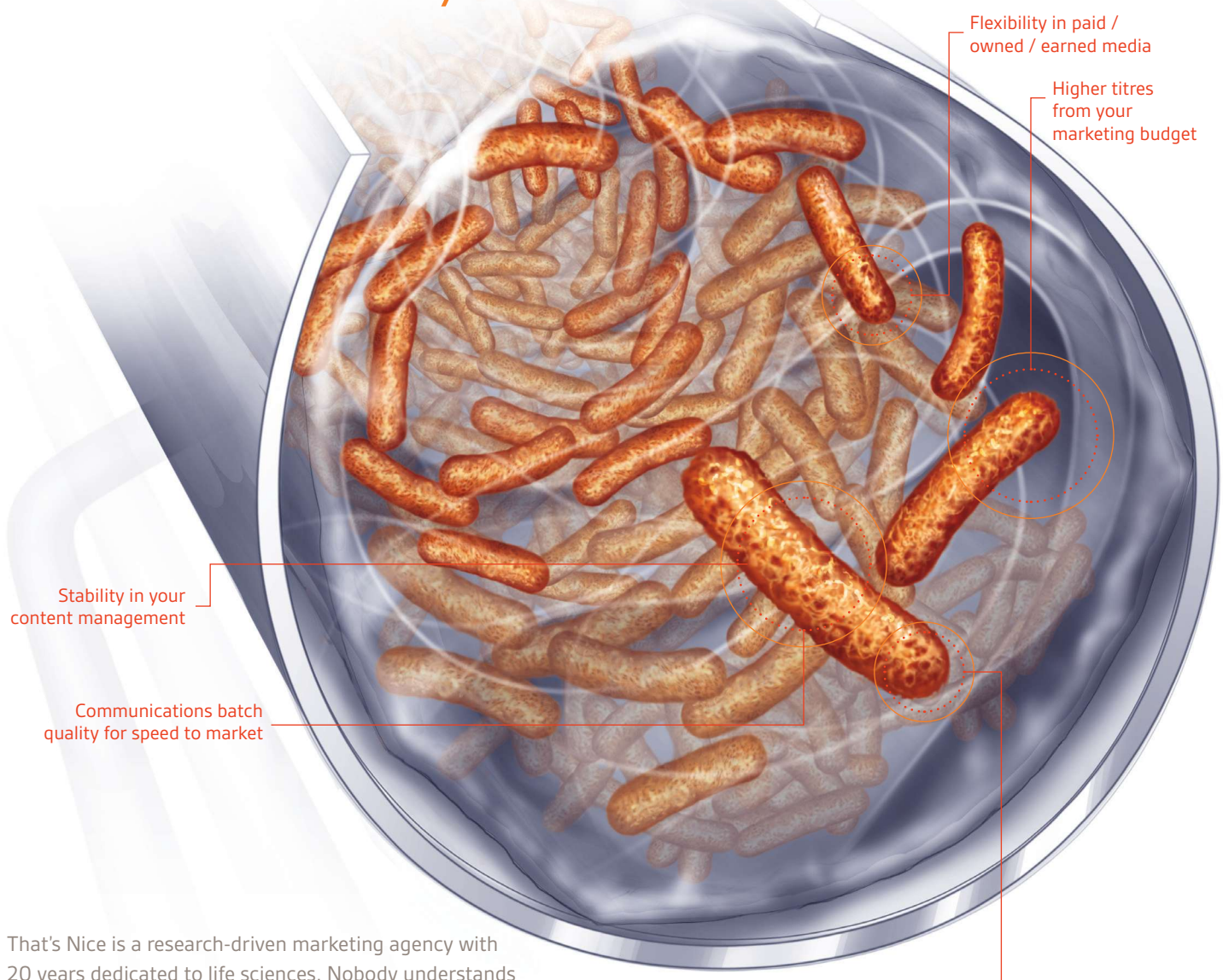

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"The objective must be active involvement of students in the knowledge transfer rather than just relying on them to read an SOP."

ALAIN PRALONG
VP, New Product Introduction & Technical Life Cycle Management, GSK Vaccines

cost pressures on biopharmaceutical manufacturing have primed development of single-use systems (SUS). Today, single-use technologies exist for almost all biopharmaceutical process applications. But capturing the inherent benefits of single-use technologies requires significant changes to current shop-floor procedures, process flow architectures, and facility layouts. While multiple studies confirmed the positive impact of SUS on capital and operational expenditures (CAPEX & OPEX), these studies also indicated that various activities normally automated in traditional facilities were again executed by operators manually when implementing SUS. This change of the shop-floor work environment driven by introducing SUS now requires adaptation of current competencies to mitigate risk of GMP noncompliance and process inconsistencies. This means replacing the current GMP compliance-driven, SOP-based push–the-button approach, with an efficient education and training approach focusing on honing operator competencies and skillsets.

Many activities executed in biopharmaceutical facilities are very similar to — and/or as regulated as — the ones carried out in industries such as food processing or aircraft maintenance. These other industries commonly employ apprentice programs to help quickly educate their operators. For example, Kraft foods has developed two- and four-year apprentice programs where students learn (from mentors and in classrooms) how to maintain either complex manufacturing equipment or to run high-volume manufacturing processes. Student skills are honed to enable them to contribute immediately and meaningfully to the business.

This kind of success further supports the implementation of apprenticeships in the biopharmaceutical industry. As outlined earlier, current approaches are fulfilling GMP compliance despite being unsuccessful with risk mitigation and process consistency. Therefore, novel, simple personnel education and training methods that bridge the gap between proven apprenticeship methodology and GMP requirements/constraints are required to move away from the current situation.

PARADIGM SHIFT IN PERSONNEL TRAINING AND EDUCATION

Over the last few years, training and education programs have been developed that don't put a manufacturer's GMP compliance at risk but still significantly increase operator capabilities and maturity. The approach consists of three tiers that are interconnected through enriched interactive ebooks and dedicated videos showing the activity to be executed in its process conditions and context of the manufacturing environment. Each activity is broken down into key steps along with process logic and timing.

TIER ONE: EDUCATE THYSELF

In the first tier, students are educated at their own pace by watching training videos and using ebooks related to their job function(s) as often as needed to help gain ownership of the tasks. Following this self-education, students review the content under supervision of a trainer. The trainer can stress specific and important information to take into consideration while assessing a student's learning curve. This step can be done face to face in workshops or through a Web-based platform. Quizzes made up of OJT images and videos help trainers further assess and validate each student's learning success.

TIER TWO: EMBED INTO QUALITY MANAGEMENT SYSTEM

In the second tier, the content of the video is transformed into a series of pictograms identifying the relevant steps. The pictograms create the link between the SOP and the lessons learned in tier one.

TIER THREE: SIMPLIFY ACCESS AND GMP COMPLIANCE

In the third tier, a sticker showing the most important pictograms of the illustrated SOP is placed directly at the point of use. This approach ensures operators have access to the most relevant information of the activity each time they execute it. Furthermore, these stickers allow trainers to educate and train students on the shop floor, leveraging the knowledge transferred in tiers one and two.

THE PATH FORWARD

The biopharmaceutical industry has embarked on a dead-end street when it comes to personnel education and training. The current training approaches have exposed the industry to significant risks of GMP noncompliance and process inconsistencies priming enforcement actions from regulatory authorities.

A paradigm shift is required that is inspired by methodologies proven in other highly regulated industries that ensure first-time-right success and process robustness by reducing operator error and process inconsistencies.

The objective must be active involvement of students in the knowledge transfer rather than just relying on them to read an SOP. Furthermore, trainers must act as craftsmen, tailoring knowledge transfer to each individual's capabilities and needs. This approach makes trainers responsible for successful knowledge transfer, which is significantly different from the typical well-documented, "GMP-compliant" ex-cathedra teaching.

Precision Oncology: Big Data And Analytics Come To Cancer Care

DR. GEORGE POSTE

Dr. George Poste is vice chairman of Caris Life Sciences and director of the Complex Adaptive Systems Initiative at Arizona State University.

Cancer care is creating a new era of precision oncology. Profiling the molecular alterations in a patient's tumor can identify changes that correlate with likely response or resistance to particular therapies. This type of molecular profiling also can lead to more precise treatment, replacing historical "one-size-fits-all" approaches. Advanced analytical technologies are revealing how different genetic mutations in cancer disrupt the molecular signaling (information) pathways that regulate normal cell function and produce specific pathway alterations in different cancers, subtypes of the same malignancy, and individual patients.

There's no doubt that a spectrum of tumor-profiling technologies is needed to provide oncologists with the most comprehensive information on which to decide treatment options. Comprehensive molecular profiling of this kind is data-intensive, already generating up to a terabyte of data per patient. Refined insights will also come from comparison of individual patient data with the profiling and treatment response data from larger patient populations and from using large-scale analytics to iteratively improve the accuracy of actionable drug to molecular target associations. Thus, adoption of molecular profiling as a routine standard in cancer care will require sophisticated annotation, analysis, and secure curation of petabyte- and potentially exabyte-scale databases. The opportunities for market expansion are dramatic, but making this a reality will involve a complex interplay of technical, clinical, and economic forces.

The bottleneck no longer resides with profiling technologies; the challenge today is the data processing and corresponding analytics (e.g., identifying new molecular targets for diagnosis, prognostic assessment, and treatment selection). In turn, leveraging the full value of profiling requires integration with a patient's clinical history and lifestyle data. Doing so helps identify confounding factors that may alter severity of disease and/or therapeutic responses. Currently, however, these data sets are fragmented in disparate systems often with incompatible formats that limit facile interoperability. Additionally, most electronic medical records are not yet designed for seamless extensibility to accommodate large volumes of diverse molecular profiling data.

This rise of Big Data in clinical medicine has created the need for new education and decision-support tools for physicians and payers. It is impossible for these stakeholders to remain aware and interpret the exponential growth in published literature. New services for literature aggregation, analysis, and ranking services will be required to set, and constantly update, evidentiary criteria for treatment and reimbursement decisions, together with automated tools to guide clinical decisions.

More than 1.5 million new cancer cases will be diagnosed and over 800,000 cancer patients will die in the U.S. in 2014. The value proposition for molecular profiling in cancer, as in other data-intensive settings, is the generation of accurate, patient-customized, actionable information that enables physicians and patients to make better–informed, real-time care decisions. Oncology has been in the vanguard of molecular profiling, but the value is not limited to cancer and extends across the entire spectrum of human disease, including profiling neurodevelopmental disorders that arise during fetal development. In addition to providing the intellectual foundation for precision medicine to improve patient care, the economic case for molecular profiling is equally compelling. By enabling high-cost treatment to be directed to only those patients likely to benefit and by eliminating futile interventions, molecular profiling can help determine how to balance infinite demand for care versus finite resources and how to control cost while improving patient care and outcomes.

What Kind of Environment Do You Create As A Leader?

MINDY HALL, PH.D.

A recent client of mine — we'll call him Eli — was transitioning into a new role in a new company. After several months on the job, establishing and immersing himself in the new culture, he asked me to collect some feedback on his colleagues' opinions of him.

As I spoke with his global team, it quickly became clear that Eli was making quite a positive impact. What I heard time and again was how "present" he was in his interactions. He wasn't checking messages or looking at his watch; he displayed genuine interest in what they had to contribute. His team members felt listened to and valued, and, consequently, they were becoming more willing every day to contribute at higher levels.

Can you say the same of your leadership? Are you aware of the environment you create? Does it inspire people to be their best? If I asked those who work around you, for you, and for whom you work to describe how you "show up," what would they say? People are watching: Are you intentionally choosing your behavior or leaving its impact to chance?

OWNING YOUR IMPACT

You are 100 percent responsible for the tone you set. You have the ability to tailor your approach, your message, and your actions to shape the outcome. You must, therefore, begin to see that the primary tool for achieving high-level results is you, as opposed to elements outside of you—such as business models, organizational structure, other people, or circumstances.

Developing this aptitude is possible and begins the moment you look in the mirror and reflect on how you show up, how you affect a room, and what environment you create. Consider the following:

- HOW WOULD YOU LIKE OTHERS TO DESCRIBE YOU AS A LEADER? WHAT DO YOU DO TO EMBODY THAT?
- WHAT KIND OF EXAMPLE DO YOU SET FOR OTHERS?
- HOW DO YOU ENTER A SPACE? DO PEOPLE PERCEIVE YOU AS CYNICAL, POSITIVE, DETACHED, PRESENT, DEFENSIVE, SCATTERED, FOCUSED?
- HOW DO PEOPLE PERCEIVE YOUR LISTENING SKILLS? DO YOU LISTEN TO OTHERS OBJECTIVELY?
- HOW DO YOU HANDLE MISTAKES THAT YOU MAKE? MISTAKES THAT OTHERS MAKE?
- HOW OPEN ARE YOU TO CHANGING WHAT ISN'T WORKING?
- THINK OF THE LAST THREE MEETINGS YOU ATTENDED. HOW DID YOU SHOW UP? WHAT DID YOU SIGNAL WITH YOUR BEHAVIOR? WHAT DID YOU CONTRIBUTE? WHAT DID YOU DIMINISH?

During the next interaction you have, choose consciously, deliberately, and intentionally the environment you want to create. Notice yourself: Be in the moment and watch yourself in the moment. How would you interpret your actions if you were on the receiving end? Create a moment-to-moment awareness that allows you to pivot, shift, and adjust. Operating with this level of intention is counterintuitive to how we live our lives, which is why it is so easy to lose sight of its importance. However, with this awareness in place, success becomes a matter of habit. L

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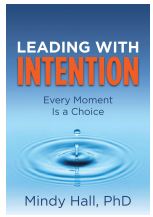

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