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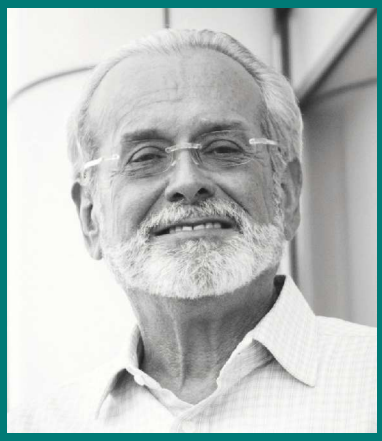
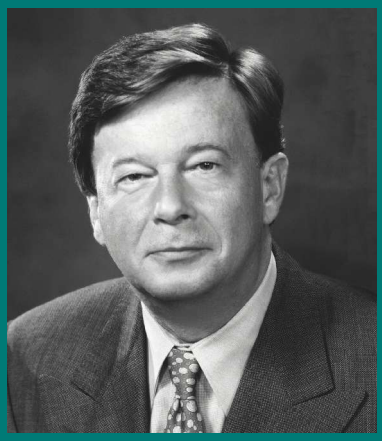



Insights From 6 Retired CEOs

Sage Advice From Industry Veterans On Balancing Biopharma's Bright Future Against Its Tarnished Image. p. 16

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In Memoriam Of One Of **Biopharma's Great Mentors**

ROB WRIGHT Chief Editor

It was the fall of 2016 when I began pursuing the idea for this month's cover feature: Interview a group of former CEOs to gain their perspectives on our industry's extremely bright future balanced with its currently tarnished image. What advice might these mentors have for today's current industry executives on drug pricing, corporate culture creation, and so much more? But on Friday, May 12, 2017, the project turned bittersweet as one of the participants, Henri Termeer (71), died after collapsing in his home in Marblehead, MA.

I first shared my vision for the article with Termeer after he spoke on a panel at the 2017 Biotech Showcase in San Francisco. It was there that the former chairman, president, and CEO of Genzyme agreed to participate. In late February we had an hour-long conversation in which Termeer answered my questions very candidly. When asked what he missed about no longer being a CEO, he chuckled and replied, "I don't know if you've noticed, but I'm very excited about this chapter in my life." He went on to highlight many of Genzyme's great moments but also its challenges. Throughout it all he said he had no regrets and seemed proud of what the company had achieved. For example, he noted the role he and his former company played in mentoring future life sciences leaders. One such leader was David Meeker, whom Termeer had groomed to take over the top position at Genzyme. I invited Meeker to share a short story about his former mentor.

"Henri bet on people as much — or more — than he bet on the science. I entered Genzyme as a medical director in the R&D organization. After six years, he sponsored my move to the business side, sending me to Europe to lead the Rare Disease BU in Europe. I had no formal business training, and in fact, had spent remarkably little time in the operating units. But I understood the science, and I understood the diseases we were trying to treat. Henri saw something in that. And I was by no means unusual. We had a remarkable executive team where many of the individuals would be classified as unorthodox choices for the roles they were in. Henri was an unorthodox thinker, and he managed his people the same way."

But Meeker wasn't the only success to surface from Genzyme. "I am told that 40 new biotech CEOs came out of Genzyme after the transaction [with Sanofi]," Termeer shared. "They call, we meet, and have reunions at JPM." He went on to say that there was nothing he missed about being a CEO. "I didn't step back," he clarified. "I stepped into a different terrain, with a lot of excitement still happening." For example, in retirement Termeer served as a company founder of four companies and served on 14 corporate and nonprofit boards.

One of the great insights gained from the experience of interviewing Termeer, as well as the five other biopharmaceutical industry icons, is that for many biopharmaceutical executives, retirement is just an illusion. For these leaders still have so much to offer our community, and the sudden passing of one like Termeer leaves a void we all struggle to fill.

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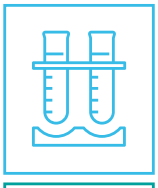

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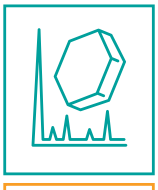

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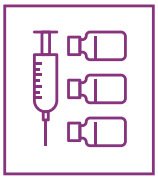

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Q How can we address some of the challenges confronting our industry (e.g., pricing, R&D spending, industry image) and gain a competitive advantage?

A IN BIOPHARMA, we've always had to quickly assess, adapt, and persevere amid changing market forces. The inherent uncertainties associated with discovery, R&D, clinical trials, globalization, and regulatory actions are all parts of our industry's robust risk assessment analyses. What has changed, though, is the pace of change. We are now compelled to more quickly rebalance our value proposition to reflect an evolving mix among healthcare costs, access to care, and outcomes.

Fortunately, today we have more information than ever before about disease states, patient populations, costs, and outcomes. Biopharma leaders are embracing tools like Big Data analytics and real-time research methods to find their new competitive advantage. We can no longer afford to study the changing marketplace from the shore; we must be in the boat adeptly navigating through the challenges confronting us.

RON GUIDO
is the president of LifeCare Services, LLC. He founded the consultancy specializing in healthcare marketing, brand protection, and supply integrity after having spent 36 years as an executive at Johnson & Johnson.

Q What was one of your most difficult learning experiences as a manager?

A IT HAPPENED WHEN I HAD TO OVERSEE consolidation of some business operations that included a large layoff. I personally knew everyone affected, so this was especially difficult. At that time, most layoffs were implemented without any advance notice to the employees who would be affected. Advisors told us that acting quickly and having people leave the same day they were laid off was the best way to minimize risk of workplace disruption or sabotage. Instead of that approach, I decided to communicate extensively about the timing and extent of expected layoffs. We also gave employees enough notice so that they could take time saying goodbye to colleagues, which was good both for people who left and those who stayed. The experience confirmed for me that the most difficult situations are best faced with transparency, communication, and respect.

RACHEL KING
has nearly 30 years of experience in various management roles in biotech and pharma. In 2003 she cofounded and became CEO of GlycoMimetics, a publically traded biotech company in Maryland.

Q How do you do demand versus capacity long-range planning?

A LONG-TERM CAPACITY STRATEGIES involve a range of assumptions and predictions about product demand, technological innovations, and the shifting competitive landscape. The forecasted growth and variability in demand, in combination with the confidence in those predictions, are core parameters. For example, when demand is more uncertain (e.g., during a new product launch), a larger "buffer" should be available. Pay attention not just to how much capacity is needed but also to what type is required and how it will be measured. Workforce capabilities often are more important when determining plant capacity than facility size or equipment output. Timing for adding/reducing capacity, and by how much, also needs to be considered. Is the strategy to stay well ahead of demand and never run short or maximize utilization and bring new capacity on just-in-time? While delaying expansion can clarify the capacity picture, the risk and impact of falling short (compared with having underutilized plants) should be weighed carefully.

SANDRA POOLE
is a former EVP of technical and commercial operations at ImmunoGen and SVP, biologics manufacturing at Genzyme.

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Path Forward
On Obamacare Replacement?

JOHN MCMANUS The McManus Group

After the House of Representatives passed The American Health Care Act — the bill that would replace Obamacare — by a razor-thin margin, consideration moved to the Senate, where Republicans have only two votes to spare to secure passage.

At an unusual White House rose garden ceremony celebrating House passage, only the first step in the legislative process, President Trump called the legislation "extremely well crafted" and a "great plan" that will end the "suffering" and "ravages" of Obamacare. Forty days later, while meeting with Senate Republicans, he characterized that same bill as "mean, mean, mean," one source told the AP. Another said the president used even more colorful language, characterizing the bill a "son of a bitch."

Perhaps a more analytical view of the impact of the major components of the bill would be more useful in guiding deliberations, as the president observed, "Nobody knew healthcare could be so complicated."

DOES THE HOUSE BILL TERMINATE COVERAGE OF 11 MILLION LOW-INCOME INDIVIDUALS WHO GAINED COVERAGE THROUGH MEDICAID EXPANSION BY 31 STATES?

No. Those individuals will continue to be covered at the 90 percent federal matching rate established by the Affordable Care Act indefinitely. The House bill merely halts further enrollment of new individuals at that high matching rate.

The debate now occurring in the Senate is how much longer *additional* non-elderly, nondisabled poor adults will be allowed to enroll at the 90 percent federal rate. The core Medicaid population — children below the poverty level, poor pregnant women, and poor elderly and disabled (i.e., a more destitute population who generally cannot work) — is subsidized at just 57 percent, on average, by the federal government. Some conservatives wonder why the federal government would provide greater assistance to individuals with higher incomes and the capability of working than to the core populations Medicaid has covered for years.

WILL THE HOUSE BILL CAUSE 14 MILLION PEOPLE TO LOSE COVERAGE NEXT YEAR?

No. This Congressional Budget Office (CBO) projection is based on its behavioral assumption that millions would immediately drop coverage due to the repeal of the individual mandate tax, which applies to individuals who do not have health insurance. This projection is based on the bizarre assumption that 5 million Medicaid beneficiaries will quit free healthcare due to the absence of a mandate that never applied to them. It never applied to them because they do not have income sufficient to pay taxes.

CBO predicts another 8 million individuals would drop coverage in the nongroup market in 2018 — i.e., *two years before* the bill makes any change to the current means-tested subsidies that substantially reduce the cost of health insurance for these individuals. Why would 8 million people voluntarily terminate heavily subsidized insurance policies?

In short, assumptions of a mass increase of the uninsured due to repeal of the individuals mandate tax are specious and unfounded.

DOES THE HOUSE BILL "GUT" MEDICAID BY CAPPING SPENDING?

No. CBO projects the House bill will reduce Medicaid spending by $834 billion over 10 years compared to its baseline estimates, prompting Senator Chris Van Hollen (D-MD) to label it an "unconscionable attack" on

Medicaid since it would cap federal payments that are sent to states for the program. It is true that the House bill would reform Medicaid by ending the open-ended federal funding for the program and establishing "per capita caps" for each patient population in Medicaid. Under the proposal, spending at current rates would be limited to Medical CPI (Consumer Price Index) for nondisabled adults and kids and medical CPI plus one percent for the disabled and elderly population.

Doug Badger and Grace-Marie Turner of the Galen Institute unpack the House proposal and estimate that Medicaid annual per capita growth spending would be slightly restrained — dropping from 4.4 percent under current law to 4.2 percent under the House bill. Most of CBO's projected savings are derived from its estimate that there will be 14 million fewer enrollees by 2026 due to the repeal of the individual mandate and termination of the 90 percent federal match for *future* state expansions to noncore Medicaid beneficiaries, notwithstanding the fact that 19 non-expansion states have debated this issue thoroughly over the past seven years and are unlikely to change their approach any time soon.

IS THE CBO PREDICTION THAT 23 MILLION MORE INDIVIDUALS WILL BE UNINSURED RELIABLE?

No. CBO's record of making these admittedly difficult projections is poor. CBO predicted 24 million would be enrolled in exchange-based coverage this year; but less than half (10 million) are actually enrolled. Even as major insurers continue to bail out of the program, CBO continues to predict ample enrollment growth in this collapsing market. A couple weeks ago, Anthem announced it would be exiting Ohio, leaving the Buckeye state with no insurer for 18 counties. This is a substantial development. Katherine Hempstead, as senior adviser at the Robert Wood Johnson Foundation, in an analysis earlier this year wrote, "Anthem is the most significant Obamacare market participant."

Muddying matters further is the independent Center for Medicare and Medicaid Services Office of the Actuary analysis released on June 12, which predicts that about 10 million more people would have coverage under the House bill than CBO predicts. That is still a reduction in coverage but a lot less than CBO's analysis suggests.

HOW CAN THE SENATE IMPROVE THE AHCA AND PASS A BILL?

Notwithstanding the hyperbole and misunderstandings of the House bill, the legislation can certainly be improved in several achievable ways by the Senate. The following are a few examples:

- Increase the $2,000 to $4,000 age-adjusted tax subsidy for the purchase of insurance in the exchanges, particularly for low-income individuals. An individual with a modest income cannot purchase a policy worth anything for $2,000 — the deductibles could approach or exceed their entire annual income.
- Eliminate the requirement that new Medicaid beneficiaries must reenroll in Medicaid every six months. This creates unnecessary churning and risks losing coverage. Annual elections are typical in the private sector and Medicare Advantage and should apply to Medicaid.
- Allow states a two-year transition period to sign up new Medicaid enrollees at the 90 percent federal rate. The expansion is only three years old, and no reasonable argument can be made that an individual meeting this demographic criterion could not sign up in a 5-year window, and nonexpansion states would be provided two additional years to grab this federal pot of money.
- Provide additional resources for opioid addiction treatment and prevention to combat a scourge that is ruining the lives of millions, particularly in working-class communities. This is a priority for Senator Rob Portman (R-OH), an influential member on the Finance Committee, and with wavering moderates in the Senate.
- Delay relief of the repealed ACA taxes (on particular health industries and higher-income individuals) until 2018, freeing the resources of the House's retroactive bill to fund the aforementioned priorities. The pharmaceutical industry would still benefit from an elimination of its $3 billion annual fee but not until next year.

Such a package would still give conservatives what they fundamentally want — a rollback of the most onerous provisions of Obamacare and a phased-in approach that minimizes disruption of uprooting a very complicated and far-reaching law. 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.

The Biotech CEO — It's Not For Everyone

KEN MOCH

I've often described the challenge of developing new medicines as analogous to the difficulty of climbing the highest mountains on Earth. If one follows that analogy, then seeking to develop a new treatment for Alzheimer's disease is like climbing K2, the second highest peak — in winter. That feat has not yet been accomplished, and those who aspire to do so describe it as their last frontier. Similarly, the brain is one of the last frontiers in medicine and drug development.

As has been demonstrated by the plethora of failed drug development efforts in Alzheimer's disease, Parkinson's disease, schizophrenia, depression, and other neurological disorders, our understanding of how the brain works is in its infancy. Conducting research and clinical development on an indication as rife with failure as is Alzheimer's disease is certainly one of our greatest challenges. Everyone involved — from scientists to patients to regulators to investors — needs to be exceptionally risk tolerant. The few medications that have been approved can slow the progression of the symptoms of Alzheimer's, but none are truly disease modifying. To add to the skepticism in the field, recent well-publicized failures — solanezumab, bapineuzumab, verubecestat — draw into question the underlying theories of the cause or causes of Alzheimer's disease.

It's not surprising that so many of us have been personally affected by Alzheimer's disease. It is this personal connection that has motivated and continues to inspire interest from investors, scientists, regulators, and patients to strive for a solution.

WHY I ACCEPTED THIS NEW CHALLENGE

There were three factors that drove my decision to take on this new position.

First, I have been fortunate to have been involved in founding and leading a number of pioneering companies, including the first liposomal drug delivery company and the first cord blood stem cell company. For this reason, I have become accustomed to being told that "No one has done that before." I have learned to live with the ambiguity and uncertainty that is drug development within a small company, and I find the challenges and potential of building a new company to be invigorating.

Second, I wanted to be involved in another company that had the potential to change medical practice and truly improve lives. While the industry has demonstrated an increasing focus on rare diseases and orphan drugs, I felt that this was the right time in my career to take on a major disease that directly impacts a large population.

The third reason is the scientific founder of Cognition, Dr. Susan Catalano. I was immediately enthralled by her passion for her mission and the intensity with which she was working to accomplish her goals. In the face of all of the odds against her, she drove Cognition from an idea to a clinical stage company. That's the type of innovative, committed person we all should support.

THE CEO'S TOP PRIORITIES

As a CEO, I consider my prime responsibilities to be four-fold: 1) to paint a vision of the future of the com-

pany 2) to ensure that the company has the human and financial resources to accomplish that vision 3) to set standards of performance and 4) to audit performance against those standards.

It was clear early on that we needed to focus on a key set of tasks in order to differentiate ourselves and "paint a clear vision."

> *"This is the first time I have managed a predominantly virtual company with key executives and consultants living in different cities and states."*

Our top priorities, therefore, were to further elucidate and differentiate our mechanism of action and to craft a financial and business plan for the company, both of which will support future fund-raising efforts. Further, we are deepening our relationships with our scientific advisors, thereby expanding the core team who can talk openly about our scientific strategy. These relationships will not only validate our scientific premise but also will be crucial as we make progress in our goal of advancing our small molecule therapeutic through clinical development.

Drug development is a team sport, and one needs the correct players to succeed. In a small company such as ours, we needed to find contractors, consultants, and advisors who could provide the experience and intellectual content to make sure we are appropriately progressing our lead molecule. Happily, many were already working with us.

EARLY LESSONS LEARNED

I think the superordinate learning experience relates to communication — within the team, with the board, and with current or future investors and partners.

This is the first time I have managed a predominantly virtual company with key executives and consultants living in different cities and states. Going back to my belief that drug development is a team sport, it was critical that everyone have a profound familiarity with the skills, experiences, perspectives, and personalities of their key colleagues. For me personally, that meant immersion not only in our science but also in the personalities of the team members. I have focused on making sure we communicate with one another frequently and that we meet face-to-face as often as possible in order to reinforce our relationships, work through challenges, and make plans for the next stages of our evolution.

With the board, it is important early on to begin to paint that "future vision." How do you convert a belief in the potential of the company into an increasing possibility of success? This involves introducing the company to your existing network, pressure testing the positioning with as many independent thinkers — scientists, investors, bankers, etc. — as possible, to see what needs to be done to build a company that will hopefully provide an extraordinary return.

While not a new lesson, it was also clear that a lot of legwork would be required to increase the awareness of and interest in Cognition with the universe of potential investors and partners. Luckily, there are many more venues in which to interact with investors and partners than there were in the early days of this industry. The key lesson, not new to my current position, is that one needs to be focused from day one on building and expanding these relationships.

A VOLATILE AND RISKY ENVIRONMENT

I often describe a biotech company as a research and development pipeline unencumbered by revenue. Biotech companies sustain themselves via the sale of equity or through milestone payments achieved in partnerships but not through ongoing revenue. Couple this with an understanding that the complexities that inevitability occur along the drug development path are magnified — the highs may be higher, but the lows are also lower. These factors make this industry unique and can be uniquely stressful. Every executive of an early-stage biotech, and every employee for that matter, has to understand their own level of risk tolerance. If you are not prepared for this type of volatile and risky environment, then being at a biotech may not be the right fit for you.

This is an industry of extraordinary potential to make meaningful changes in the quality and quantity of life, but this fact is counterbalanced by the complexities of bringing these new medicines to market. That being said, the psychological reward of shepherding a new drug from development to approval after years of hard work, and of seeing people live who otherwise might have died, is extraordinary. So perhaps the most crucial consideration for an executive is: What motivates you to go to work each day? L

KEN MOCH is the president and CEO of Cognition Therapeutics. He has broad expertise building, financing, and leading private and public life science companies from start-up through commercialization, having previously served as president & CEO of four life science companies.

GeNeuro

Fighting MS and other diseases through a novel target – human endogenous retrovirus expression

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

GeNeuro is developing drugs for targeting a novel disease mechanism that is directly causal, not one indirectly related to the disease symptoms targeted by conventional drugs: human endogenous retrovirus (HERV) expression. GeNeuro's lead program, for the drug coded GNbAC1, is in a Phase 2b trial for treating relapsing remitting MS, conducted in partnership with Servier, with six-month data expected in October this year. GNbAC1 is also in Phase 2 trials for Type 1 diabetes, with results expected in the second half of 2018.

WHAT'S AT STAKE

Several years ago, we published the "Hot New MoAs in Neurodegenerative Disease" series, covering Alzheimer's, Parkinson's, and MS in three respective parts. No one among the MS opinion leaders mentioned endogenous retroviruses in the discussion. Indeed, one of GeNeuro's main challenges is overcoming skepticism or ignorance about its unique approach to MS and other conditions.

As our series described, the main target of treatment for MS for many years has been inflammation due to unrestrained innate immune response — and that was where the thought leaders still pinned most of their hopes for new and improved therapeutic agents. Fighting MS has become synonymous with suppressing the immune response by inhibiting the immune system, then trying to limit the treatment's inevitable toll on the body.

Eons ago, endogenous retroviruses infected and inhabited the human genome, and they normally sit dormant until activated by something like a herpes infection, when they can express harmful proteins and cause disease. In MS, the research shows the human endogenous retrovirus-w (HERV-W) family encodes MS-associated retrovirus envelope protein (MSRV-Env), which promotes inflammation and myelin loss in neurons. GeNeuro designed GNbAC1, a humanized mAb (monoclonal antibody), to block the protein's pro-inflammatory and anti-remyelination effects at the disease site.

"This dual mode of action through targeting a potential causal factor, relevant in all forms of MS, without affecting the immune capacity of the patients, makes this approach truly unique," says Jesús Martin-Garcia, GeNeuro's CEO. "MSRV-Env has been shown to be a pathogenic protein and has no known physiological function. Therefore, it is expected that GNbAC1 will have a very favorable safety profile, as evidenced in clinical trials to date."

Outside skepticism about GeNeuro's scientific concept has made fundraising even harder than usual for a startup. But the Swiss company has found considerable support in Europe thanks to two main factors, Martin-Garcia says. "We had visionary early-stage investors who recognized the value of the scientific research emerging from Institut Mérieux and INSERM, as well as the potential disruptive nature [of GNbAC1] if translated into therapeutic applications."

GeNeuro remains the only company doing clinical development based on HERV expression, but Martin-Garcia says academic scientists are identifying potentially new links to disease at an exponential rate. He cites the company's many collaborations as well, such as a CRADA agreement with the NIH to develop a novel antibody treatment for amyotrophic lateral sclerosis. The partnership will build on NIH discoveries associating the envelope protein of HERV-K with ALS and on GeNeuro's HERV-protein antibody expertise. The company's deal with Servier will amply support the development program for GNbAC1 in MS.

Like many startups emerging from preoccupation with their scientific mission, GeNeuro is now turning some belated attention to explaining itself to the world. "With hindsight, we had certainly not dedicated enough time to making this novel area more accessible and easier to understand," says Martin-Garcia. "Now we are making considerable efforts to communicate our novel approach, but the key remains the data we will generate through clinical trials." True enough. Words may carry meaning, but the data must agree.

JESÚS MARTIN-GARCIA
CEO

30
Employees

Headquarters
Geneva, Switzerland

Finances

VC Rounds
CHF 29M

Lead Investors
Eclosion2,
Institut Mérieux,
Servier,
BioMérieux

IPOs
€33M

Research Partnership Funding

Servier
€362.5M partnership development, potential commercialization of GNbAC1 in MS outside U.S. and Japan

Other Partners

NIH CRADA
(Cooperative Research & Development Agreement) to develop novel therapeutic antibodies for amyotrophic lateral sclerosis

Latest Updates

June 2017:
Data on role of HERV-W Env and GNbAC1 in Type 1 diabetes presented at the Annual Meeting of the American Diabetes Association

April 2017:
GNbAC1 Phase 2a study in Type 1 diabetes initiated in Australia

January 2016:
GNbAC1 Phase 2b study in MS fully enrolled

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Balancing Biopharma's Bright Future Against Its Tarnished Image

Insights From 6 Retired CEOs

ROB WRIGHT Chief Editor

Editor's Note: On May 12, 2017, former Genzyme CEO Henri Termeer passed away unexpectedly at his home in Marblehead, MA. The man who considered himself a "biotech entrepreneur" was actually the first executive to be interviewed for this feature (February 27, 2017). Prior to his passing, Termeer reviewed this, as well as the two additional articles developed from our conversation that appear in the "Beyond The Printed Page" section of our publication. We at Life Science Leader mourn the loss of an industry icon who gave so much to biopharma.

Francois Nader knows of dark days. "When I joined NPS [Pharmaceuticals] we downsized the company from 450 people to 17," he says. The company's former CEO admits that was one of his most hated days as an executive, and he vowed never to put either himself or the company in a situation where he'd have to do that again. But the 30-year biopharma veteran knows of many more bright days, such as being at the helm of NPS when it was acquired by Shire for $5.2 billion. Today Nader is considered "retired," a word he prefers to qualify. "I don't think any one of us is technically retired," he says in reference to the prolific group of former CEOs assembled for this article. "There is so much we all are still trying to do."

At *Life Science Leader*, we not only wanted to find out what life is like after retiring from a pharma CEO role but also what some of these leaders have to say now — unrestrained by corporate lawyers and PR teams — about the current state of the industry. What would they do differently? Whom are they still mentoring, and what are they advising?

We successfully connected with the following six former CEOs: Mike Bonney (Cubist), Hank McKinnell, Ph.D., (Pfizer), Francois Nader, M.D., (NPS Pharmaceuticals), David Pyott (Allergan), Stephen Sherwin, M.D., (Cell

Genesys), and Henri Termeer (Genzyme). As Nader previously noted, all of these men are anything but retired; they are all current members of numerous corporate and nonprofit boards and quite active in mentoring. What follows are their thoughts on the biopharmaceutical industry, drug pricing, and so much more.

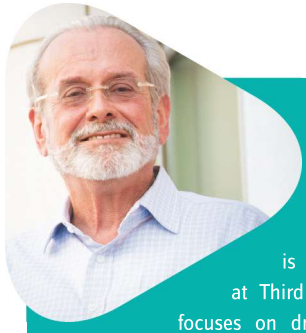
A BOARD-LEVEL PERSPECTIVE ON BIOPHARMA'S FUTURE

The first question posed to each executive was how they see the biopharmaceutical industry performing during the next five years and then the five years after that. The consensus was overwhelmingly positive. Stephen Sherwin believes the next 10 years in biopharma will someday be looked upon as the "golden age" of biomedical research. But as Hank McKinnell notes, it is what is being done today that is setting the table for biopharma's future. "Our industry is unusual in that we have 12- to 15-year lags in product discovery and development," he shares. "What we are seeing today is a reflection of the state of the industry a decade or so ago." As an example he cites the mapping of the human genome in April 2003. "Though a massive effort was applied to utilize this new genomic information, only fairly recently we have begun to see progress, which is in large part due to the advancement of new technological tools."

Mike Bonney envisions biopharma's future involving both headwinds and tailwinds. "Headwinds derive from the political process and focus on pricing and access," he states. "Tailwinds are the spectacular progress being made in our understanding of human biology." While Bonney believes the industry will work through a more transparent (and potentially more rational) pricing scheme, he sees a challenge resulting from a supposed tailwind. "It is always difficult to predict when insights will translate into something that meaningfully affects human disease," he shares.

Francois Nader believes that one of the keys to addressing Bonney's expressed concern will be the combination of data and technology. "Clinical development remains the backbone of everything we do," he states. "But the way we run clinical development [i.e., traditional Phase 1, 2, and 3 trials] will evolve in a pretty dramatic way." This transformation will be the result of having significantly more data and the emergence of biomarkers that will change the way drugs are monitored in the human body. "But even more important will be a greater reliance on nonhuman assessment of drugs," he continues. "I see animal models and lab work evolving in such a way that we won't be doing 10,000 to 30,000 patient clinical trials anymore." Nader anticipates new technologies providing answers as to how a drug will work long before being given to humans in clinical trials, which will significantly reduce risk and drug development timelines, as well as R&D costs.

David Pyott sees containment of skyrocketing R&D costs as one of the biggest drivers of technology adoption. "More costs being shifted to the patient has created a pressure point," he explains. Relieving this pressure will require more than lower drug prices and higher rebates. "The price of most of the goods we buy as consumers tends to go down, not up," Pyott affirms. "Biopharma will soon no longer be a privileged outlier, and healthcare in general will soon be in the same realm as most other industries." Waiting 45 minutes in a doctor's office before being seen for five minutes will be replaced by telemedicine. Wearables currently track data only in a passive way, but soon these technologies could proactively manage one's



STEVE SHERWIN

Stephen Sherwin, M.D., is currently a venture partner at Third Rock Ventures, where he focuses on drug-discovery-stage projects throughout the company's portfolio. In addition, he serves as a Clinical Professor of Medicine at the University of California, San Francisco (UCSF) and a volunteer Attending Physician in Hematology-Oncology at Zuckerberg San Francisco General Hospital. He is also a member of the scientific steering committee of the Parker Institute for Cancer Immunotherapy. Sherwin currently serves on the following company boards:

- Aduro Biotech (NASDAQ: ADRO)
- Biogen (NASDAQ: BIIB)
- Neon Therapeutics
- Neurocrine Biosciences (NASDAQ: NBIX).

Previously he was chairman and CEO of Cell Genesys, a cancer immunotherapy company (1990 – 2009) until its merger with Biosante Pharmaceuticals (now ANI Pharmaceuticals). He is also cofounder and chairman of Abgenix, an antibody company that was acquired by Amgen in 2006, and cofounder and chairman of Ceregene, a gene therapy company which was acquired by Sangamo Therapeutics in 2013. In addition to having worked at the National Cancer Institute and Genentech, he served on the board of directors of the Biotechnology Innovation Organization (BIO, 2001 – 2014), BIO chairman (2009 – 2011), and was a member of the President's Council of Advisors in Science and Technology (PCAST) Working Group on Drug Development (2011 – 2013).

HENRI TERMEER - A REMEMBRANCE

By Robert Weisman, Healthcare Business Writer, *The Boston Globe*

My introduction to Henri Termeer came during a stressful time for his pioneering biotechnology company.

I was a veteran business reporter but new to the biotech beat. And I expected the familiar CEO bobbing and weaving when I asked him about the 2009 contamination at a Boston manufacturing plant that forced Genzyme to temporarily ration its treatment for a rare disease. But his responses were forthright, focused not on the jitters of investors but on the company's determination to set things right for patients. He was similarly candid with me – and with *Globe* readers, his staff, and the wider community – throughout the months of negotiations preceding Genzyme's acquisition in 2011.

It wasn't until later that I learned Henri had been a mentor to dozens of executives who went on to run other biotechs. In that way, he seeded an industry working to discover new treatments and cures for diseases around the world. I also came to understand his contributions as a founding father of a field on the cutting edge of discovery and innovation.

For my part, I was mostly struck by Henri's openness and accessibility, a stark contrast to the posture of many other executives I've covered in crisis situations. He took my calls and answered my questions and patiently educated me about the origins and promises of biotech. He was as generous with his money as he was with his time. About six months after the Genzyme buyout, Henri and his wife Belinda donated $10 million to establish a research center for targeted cancer therapies at Massachusetts General Hospital.

Who will take the place of Henri Termeer – trailblazer, entrepreneur, and mentor – in the world of drug discovery and patient advocacy? Hopefully, one or more of the many people he guided and inspired during his career in biotechnology.

health, something we have already witnessed with insulin pumps.

When asked for examples as to what they find most exciting, there was hesitancy to pinpoint one area of science or technology. "It is the combination of technologies and sciences that are allowing us to deal with issues around assays, delivery, and diagnostics," says Henri Termeer. As for companies these executives find exciting, many defer to those on whose boards they serve, and with good reason. "Moderna Therapeutics has made amazing progress by getting a Zika vaccine into the clinic within 12 months of project origination," shares Termeer. "There is the possibility that mRNA could significantly change an expansive component of drug development." Another breakthrough cited by Termeer was the work being done by Aura Biosciences. "In a very short period of time they have been able to develop a way to treat ocular melanoma, something that had not previously been done." But perhaps the greatest example of a fantastic breakthrough comes in the area of Hepatitis C. And while these tremendous advances forever changed treatment of the disease, there was an associated shock effect, namely the price (e.g., Sovaldi's initial price of about $1,000 a pill).

When we asked Mike Bonney what he thinks could make biopharma's future even brighter, he responds, "I'd like to see the development of a predictive toxicology consortium. This would not only advance the science but would also help bring global regulators along." Bonney believes combining technology with our growing understanding of how individuals react to various types of medicines could pay huge dividends. "Under the right scenarios, existing huge databases residing inside each company could be contributing to a much broader database," he elaborates. "Utilizing Big Data techniques, we could analyze what predictive value one might get from various standard tests and identify programs where the toxicological risk is less."

ARE LOWER MARGINS IN BIOPHARMA INEVITABLE?

Not long ago, an outgoing biopharmaceutical CEO stated that the industry must get ready for lower margins as price resistance will only grow, and R&D costs are not coming down anytime soon. We asked our distinguished group if they agreed with this assessment. "Yes and no," Nader responds. "Those working to develop products that deliver marginal improvement over currently approved drugs (i.e., business as usual) can expect relatively low margins. However, the industry could potentially have higher margins if we leverage innovation." For example, instead of treating certain diseases (e.g., diabetes, hypertension, or rheumatoid arthritis) for life, what if these could be cured? If such a situation were to happen, Nader could see companies having very healthy margins.

But why do biopharmas need such high margins to operate? "It's because of the high rate of failures," Nader attests. Traditionally, for every 10,000 compounds that start in preclinical, only one makes it to approval. "But

what if we can change that proportion by increasing the probability of success in preclinical and clinical development?" he asks. "Instead of spending $1.5 billion for each new entity to make it to market, what if we spent one third of that [i.e., $500 million]." The idea is basically to double or triple R&D productivity, which sounds like an enormous task until you hear it framed by Nader. "We are talking about going from 1 in 10,000, to 2 or 3 out of every 10,000. I don't think that is too much to ask."

According to Sherwin, there's a certain inescapable cost in drug discovery for transformative therapies where we don't have precedent and are breaking new ground. "I'm not sure those costs can ever be decreased significantly, as they are a cost of scientific discovery, and I am not sure anyone can calculate that." But he agrees with Nader that the "D" part of R&D (i.e., the cost of clinical trials) is something that can be addressed. "We can do better in how we design clinical trials, determine endpoints, etc.," he affirms. "We should be looking at clinical trial design and execution with a critical eye, not just from a cost standpoint, because these trials involve patients with diseases. We owe it to them to be as efficient and balanced as possible."

In oncology, Sherwin's medical specialty, he says the field is benefitting from being able to identify segments of patient populations based on specific genetic mutations. "In some cases, not all, we have identified druggable targets and have specific therapeutics to aim at those mutations. When doing clinical trials, we can select patients with a specific mutation, which can often result in more successful outcomes derived from shorter trials with a smaller number of patients." Sherwin sees no reason a similar approach couldn't be applied in other disease areas. "I find it remarkable that there hasn't been a greater effort made to segment patient populations based on genetic abnormalities. In the next generation of sequencing technologies, people want and need the ability to gather genetic abnormalities more efficiently so patients can be identified and segmented by diseases that historically have been lumped together." Rheumatoid arthritis (RA), the most prevalent of the autoimmune diseases, is currently managed by treating just about everyone with a TNF inhibitor (e.g., Remicade). "But if we think differently and apply a precision medicine approach to addressing this and other human diseases, we can expect significant progress in medical R&D," Sherwin concludes.

From Mike Bonney's perspective, failure to improve R&D productivity threatens industry innovation at its core. "It's hard

MICHAEL BONNEY

Michael Bonney currently serves on the boards of: Celgene (NASDAQ: CELG); Alnylam Pharmaceuticals (NASDAQ: ALNY); Global Blood Therapeutics, Inc. (NASDAQ: GBT); Revolution Medicines Inc; Magenta Inc; and the Whitehead Institute for Biomedical Research. In addition, he is also a trustee of Bates College, the Gulf of Maine Research Institute, and TELKA fund complex, which focuses on healthcare investing. Bonney is a former partner of Third Rock Ventures, which he joined after retiring from Cubist Pharmaceuticals as the company's CEO in 2014.

Bonney began his pharmaceutical industry career in 1984 with Zeneca Pharmaceuticals. He held a number of positions of increasing responsibilities in sales, marketing, and strategic planning, rising to the position of national business director. He joined Biogen in 1995, eventually becoming the company's VP of sales and marketing, and was responsible for one of the most successful drug launches in biotech history, Avonex. Bonney joined Cubist in 2002 as the company's president and COO. He became CEO in June 2003, a position he held until 2014 when it was acquired by Merck for $9.5 billion.

A former board member of NPS Pharmaceuticals until its acquisition by Shire in 2015, he was also a member of the boards of PhRMA from 2009 to 2014 and BIO from 2004 to 2009.

to convince purveyors of capital to take high levels of risk and not receive relatively high levels of return," he explains. Adding to Nader and Sherwin's previous suggestions, Bonney thinks R&D productivity can be improved by working more closely with the patient/provider communities. "There is significant room for improvement via various digital resources and online communities to help clinicians and patients find the appropriate time to utilize a given intervention. In addition, we could be more productive in how we deliver medicines, particularly in the U.S." According to Bonney, a close review of just about any commercial biopharma's P&L statement reveals, over time, an enormous increase in the gross-to-net calculation. While this is made up of a variety of factors, the largest has to do with the existence of very complicated pricing schemas. "Depending on the size of the company's portfolio, a lot of infrastructure costs, whether government or private-payer driven, have been put in place just to manage things like difficult-to-administer drugs," Bonney elaborates. "A lot of that rise in gross-to-net seems to be going toward funding elements of the healthcare delivery chain that add modest value, and I think we could probably take some of those costs — not easily — out to improve/maintain margins."

Manufacturing is one of the challenges Hank McKinnell sees for biopharma regarding managing the margins. "We're moving from a period when drugs were expensive to discover and develop and very inexpensive to manufacture. Drugs are still expensive to discover and develop. However, as we take a more targeted approach to medicine, personalized (biologic) drugs can be much more expensive to manufacture." While McKinnell is also optimistic that biopharma margins can be positively impacted by improving R&D productivity, industry can't lose sight of opportunities to become ever more efficient manufacturers."

WHAT ABOUT DRUG PRICING?

There seemed to be a consensus among these former CEOs that the U.S. consumer is subsidizing global access to biopharmaceutical innovation. "Differential pricing around the world is undeniable, and it's fundamentally a trade problem," Bonney attests. "But most people responsible for constructing trade deals don't want to think about it that way." The economics of biopharma is that the costs of failure are allocated across the costs of successes and expensed as companies go along. "The marginal costs of producing most pharmaceuticals are minimal," he continues. "So once a company has gotten a new therapeutic approved and covered all of its sunk costs, it benefits by developing as broad a market as possible." Most companies prefer to first launch a drug in the U.S. because it is the largest market and an FDA approval serves as the gold standard for most other regulatory bodies. But in doing so, the U.S. consumer is placed in a position of having to pay the highest possible prices for new drugs.

"We don't currently have a good payment system for biopharmaceutical innovation," Termeer adds. "If we don't develop one, we won't get the desirable effect of innovative therapeutics for patients." Termeer believes the likelihood of progress in the U.S. is high considering that biopharmaceutical innovations are in the hands of numerous entrepreneurs and a number of large, powerful companies — not a single bureaucracy. He feels that drug pricing decisions can't be made in a corporate vacuum. "Recent drug pricing decisions by Marathon, Turing, Valeant, and Mylan were stupid. Those were bad business decisions for shareholders because they are not sustainable."

According to Termeer, any business plan that relies on being able to charge a very high price on something that hasn't been earned is a bad business plan. "It's not a right to charge a high price for the sake of giving a

higher return to shareholders as this Shkreli guy talks about," he asserts. "To shareholders, we have a personal responsibility to develop a business that grows, is sustainable, and is allowed to be in the marketplace by society because it makes a contribution that is wanted and needed." Termeer feels the response to the EpiPen pricing decision is something Mylan leadership should take to heart and never do again. But beyond the negative impact such decisions have on individual companies, it also has a spillover effect that hurts the entire industry. "If you want to build a business that is able to spend a high amount of its revenue on R&D, you need to be very critical of what you are doing and where you put your focus, because you can't do everything," he shares. "Pick a few things that are truly worthwhile and can really make a difference, and don't take shortcuts."

While McKinnell admits that the United States is being criticized for having some of the highest drug prices in the world, often overlooked is the fact that the U.S. also has some of the lowest prices. "Discounts to managed care can range from 50 to 80 percent, and in some cases drug prices can go all the way down to zero, so as to be made available to those who can't afford them," he attests. "Currently, the biopharmaceutical industry is getting the worst of both worlds [i.e., criticism for high prices and massive discounts]. There has to be a better way." Though he reminds people to be mindful of the antitrust rules (i.e., if a company wants to price its drug artificially high, then it is free to do so), fairly priced drugs in a more transparent pricing system that everybody can understand could be a useful solution. In such a scenario, McKinnell believes companies would have to justify the price based on benefit and value, and the only way intermediaries (e.g., payers) could extract additional discounts would be to deny or ration access. "I don't think any intermediary in the U.S. would be successful with a program that rations access to essential medical care. The current confusion that exists around drug pricing, combined with the criticism currently being heaped on the industry, along with the critical importance drugs have for patients, demands some new thinking that doesn't involve the innovator's losing too much to distribution-chain middlemen."

ADVICE FOR TODAY'S LEADERS

Over 15 questions were posed to this group of industry icons. And while all responses provided great insight, perhaps the most revealing were their answers to the question, "What advice do you have for today's leaders on overcoming biopharma's current image problem?"

ON COMMUNICATING EXTERNALLY ABOUT DRUG PRICING

"As an industry we are the worst communicators ever," Francois Nader begins. "Since I started my professional biopharmaceutical career, our message has not changed." Nader feels that harping on the fact that biopharma spends 10 to 15 percent of its revenues on R&D simply doesn't resonate with the public. "We need to focus on explaining how we are able to treat a condition or how we have been able to change a patient's life."

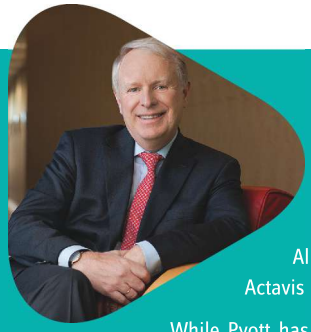
Building on Nader's point, Termeer cautions CEOs not to try to take on the task of communication with the public in isolation. "Working with organizations like BIO and PhRMA is essential," he states. "It is easy to belong and even easier to learn."

Pyott has a different opinion. "With all due respect to PhRMA and BIO, industry leaders cannot rely solely on

FRANCOIS NADER

François Nader, M.D., is current chairman of the board of Acceleron Pharma Inc. (NASDAQ:XLRN). He is also a board member of: Advanced Accelerator Applications (NASDAQ: AAAP), Clementia Pharmaceuticals, and ArRETT Neurosciences. In addition, Nader is the president of the Jesra Foundation, a trustee of the New Jersey Chamber of Commerce, and sits on the advisory board of the Open Future Institute.

From 2008 to 2015, Dr. Nader served as president, CEO, and board member of NPS Pharmaceuticals, a company he transformed into a leading global biotech focused on delivering innovative therapies to patients with rare diseases. Nader retired from NPS when it was acquired by Shire for $5.2 billion. When asked what he misses about no longer being a CEO he stated, "I loved being CEO during both good and bad days. I truly do miss it. Everyone will tell you they miss the team, which I certainly do. But what I miss most is not being at the helm of something that is designed to make a difference. You can be at the helm of anything, which is fun. But working as a leader in our industry where we are trying to make a difference for human beings is an unbelievably positive feeling."



DAVID PYOTT

David Pyott currently serves on the boards of: Avery Dennison Corporation (NYSE: AVY), Royal Philips (NYSE: PHG) in the Netherlands, BioMarin Pharmaceutical (NASDAQ: BMRN), and Alnylam Pharmaceuticals (NASDAQ: ALNY). Pyott served as the chairman and CEO of Allergan (since 2001 and 1998 respectively) until 2015 when the company was acquired by Actavis in a deal valued at approximately $70.5 billion.

While Pyott has had a very distinguished biopharmaceutical industry career that began in 1980 when he got his start with Sandoz Nutrition, perhaps his crowning achievement was the successful prevention of a hostile takeover attempt of Allergan, a company he had grown from approximately $1.1 billion in annual sales. Initiated by Bill Ackman in April 2014, the billionaire hedge fund manager and activist investor had teamed up with Valeant Pharmaceuticals (NYSE: VRX) and its then CEO, J. Michael Pearson. The initial offer was valued at just under $46 billion, a supposed 38 percent premium over the company's value. However, Pyott wasn't interested because: it significantly undervalued Allergan; he didn't believe the Valeant business model of buying companies and jettisoning R&D to be sustainable, and a significant portion of the offer was in Valeant stock, which Allergan shareholders would end up owning if a deal came to pass. For more on how Pyott succeeded in preventing the takeover, be sure to read: "Inside a Hostile Takeover: Lessons From The Allergan-Valeant War" in *Life Science Leader*'s February 2016 issue.

trade associations to carry the message." As these organizations tend to search for common ground among its members, Pyott feels the end result is messaging that is "plain vanilla." Unlike Nader, Pyott believes there is value in reminding the public just how much it costs to develop new drugs and devices. However, he feels such efforts get "blown to smithereens" in a matter of minutes by the bad behavior of a few.

In addition, Pyott advises resisting internal advice to overly water things down. "This is not to say you go out and jump off the ledge without a parachute," he continues. "You should listen to the advice of your lawyers and communications teams, but at some point you have to step out and tell a passionate and compelling story." He says it requires personal engagement to best manage the message. "People need to see the gleam in your eye that you really believe what you are doing," he attests. "I'd love to see some Big Pharma CEOs step up, stand tall, take it on the chin, be humble but not apologetic, and tell their companies' stories."

McKinnell, a former chairman of both PhRMA and the Medical Device Manufacturers Association (MDMA), agrees with Pyott that leaders shouldn't rely on these organizations to communicate the message, but he sides with Termeer in not taking an individualized communication approach. "We need a third way that works within industry associations, a group of like-minded CEOs who charter market research, think of public perceptions of industry, and find alternatives on how we might work to change those perceptions."

Sherwin, a former chair of BIO, feels that the cost of pharmaceutical products has taken on increased visibility and needs to be addressed by industry both individually and collectively. "We need to justify the value of a drug's price, which can be measured unto itself, relative to derived healthcare cost savings, or in comparison to other currently available treatments. He believes that if companies do a good job articulating the value that treatments provide, they will be better able to get fair and reasonable pricing. "When I was at Genentech, one of the drugs we brought to market was TPA, a thrombolytic agent for prevention of heart attacks in patients with acute chest pain. Think about how much money has been saved related to reduced hospitalizations due to a product like this. That's an example of how we need to consistently think when communicating the value this industry brings patients.

He admits it's much easier to say things like, "If we want innovative drug development, we have to be willing to pay high prices for drugs," because that's what drives the financial engine of drug discovery. But in his view, such an argument today falls flat. Sherwin points to governing bodies in Europe requiring price and value justification as what is likely coming to the U.S. "We can either wait until laws are passed that we may not feel comfortable with, or we can take the initiative to address an issue looming on the horizon." For example, when Sherwin was BIO chair, the Affordable Care Act (ACA) was before Congress. "One of the ACA provisions was the biosimilars exclusivity period and some other aspects of biosimilar regulation," he details. "During BIO board meetings in prior years, there was this attitude that we were never going to allow biosimilars, as doing so would kill industry R&D." But rather than fight, BIO went on the offensive, coming up with proposals for how the FDA could regulate biosimilars, which are currently in place today. "By way of analogy, we need to do the same thing on the subject of drug pricing. Sustained and continued investment in R&D requires us being able to articulate drug value and cost savings."

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ON CORPORATE CULTURE — CREATION, TRANSITION, MAINTENANCE

"Entrepreneurs have to take all kinds of risks to reach beyond what has already been done," Termeer states. When building Genzyme, the approach was to create a culture that attracted those with an entrepreneurial spirit, or as Termeer likes to say, "folks driven to do more." He explains, "We were a very purpose-driven company as opposed to a strategy-driven company. In a purpose-driven company, the process and the people matter the most, whereas in a strategy-driven company, it is the system and structure." Termeer believes that the reason Genzyme was so successful was its focus on people. "In such an environment, people view the company as bigger than themselves," he states. "From my experience, having a purpose-driven orientation is very motivational and creates that sense of motherhood and apple pie, which makes all the difference in the world."

For a deeper understanding of what goes into creating a purpose-driven company, Termeer suggests reading, *The Individualized Corporation: A Fundamental New Approach to Management* by Sumantra Ghoshal and Christopher Bartlett.

For the past 20 years, Mike Bonney has been involved in leading organizations through the transition from being development-stage companies to those with commercial aspirations. According to Bonney, as commercial issues become more prominent, so do lawyers. "You've got liability, promotional, and pricing concerns, to name just a few, and all can have a very chilling effect on employee risk taking, which is a very serious problem for small, fast-growing companies. Suddenly, risk taking that was essential when at the development stage seems overly risky for a commercial venture." Bonney comments that attorneys are trained to help manage risk, and the easiest way to do so is to simply avoid it altogether. "As senior leaders, you can't delegate all your decision making to the lawyers on staff. You want their thoughtful articulation of the rules and regulations so you can make informed decisions about where you will and won't take risks. Managing this cultural transition from development to commercial is a critical aspect of becoming a successful company."

After he left Pfizer and was mentoring younger CEOs and joining boards, McKinnell says he learned one of the most important messages he has for leaders of any organization. Inevitably, one of the leaders he would be working with would thank him and acknowledge that McKinnell could be doing many other things in his retirement. "I spent 36 years at Pfizer, and had a great and satisfying career," he shares. "But I don't recall anyone saying thank you, and I regret to admit that I as a leader, underestimated the power of that. Don't forget that everybody who works at your organization has other options, yet they chose to work with you. There is power in saying thank you and for showing appreciation."

HANK MCKINNELL

Hank McKinnell, Ph.D., currently serves as the chairman of the board of Moody's Corporation. In addition, he currently serves on the boards of ViewRay, Inc. (NASDAQ: VRAY) and ChemoCentryx (NASDAQ: CCXI). Since retiring from Pfizer as its chairman and CEO in 2007 (a company he helped to grow into the world's largest drugmaker), McKinnell has held a number of other corporate board and executive-level positions.

Having joined Pfizer in Tokyo back in 1971, he held positions of increasing responsibility around the world, including service as president of Pfizer Asia, Pfizer country manager Iran/Afghanistan, VP of strategic planning, CFO, president of Pfizer medical device group, president of Pfizer pharmaceutical group, and president and COO. McKinnell is chairman emeritus of the Connecticut Science Center; the Business Roundtable, an association of 170 CEOs of America's largest companies; PhRMA; the Food and Drug Law Institute; and the Medical Device Manufacturers Association (MDMA). Dr. McKinnell also served as vice chairman of the World Economic Forum (WEF) and as a member of the WEF Foundation Board of Trustees. He served on the President's Advisory Council on HIV/AIDS.

ON EXECUTION

"My motto in life is: To be successful, be different — exceedingly well," Nader shares. "Coming up with a brilliant idea doesn't help much if the execution [done exceedingly well] doesn't follow." NPS was developing two drugs for large indications. Nader decided to switch both to rare disease indications where there was no competition. "We succeeded in getting these approved and launched in both the U.S. and in Europe. That execution enabled us to make a successful exit and be acquired by Shire."

When he talks to young or first-time CEOs/entrepreneurs, he asks them to explain how they can run their businesses differently from their competition. "More importantly, I ask them to explain how they will do it exceedingly well." Nader says they can speak for hours about their product or technology, but when asked how they are going to actually do it, the result is often long silence. "This is when I usual-

ly hand them Larry Bossidy and Ram Charan's book, *Execution: The Discipline of Getting Things Done,* and suggest they read it."

ON SOCIAL MEDIA

Most of these CEOs admit that social media is not their strong suit, though they all do use it in various forms. "Social media is the most important tool that allows you to think completely differently about your audience in these biotech environments," Termeer stresses. "In the past, with ultra-rare diseases, it was so difficult to get in touch with these extremely small patient populations. With social media, not only can you connect with the patient population in a completely different way, but you can also stay connected." He views company leaders not becoming competent in the use of social media to be missing an opportunity that will, over time, become increasingly expensive.

McKinnell isn't sure if Twitter is the right forum for a CEO. "It may be true that you can capture headlines and get attention through Twitter and Facebook, but I'm not sure they are the right places to communicate complicated, serious messages," he explains. "It is hard for a leader to paint a vision that convinces people how great something will be in 140 characters." For internal communication he recommends (whenever possible) doing so in person. For external communication he still views television as a strong medium.

Pyott, Bonney, and Sherwin advise taking a disciplined approach when using social media. This is because use of social media can feel informal, almost like having a conversation. "In a conversation, unlike giving a prepared talk, people don't usually take a disciplined and intentional approach," says Bonney. "With social media you still have to remember that you are speaking on behalf of the company." As such, Pyott, Bonney, and Sherwin advise understanding the regulatory and legal requirements before use. Nader's tip is to ask the following questions before using it: "Why am I doing it? What's the purpose? What's my message?"

ON LEADERSHIP

One of the questions posed to all of these executives was whether they found a particular tool useful to becoming a better leader. Mike Bonney referenced *Team of Rivals* by Doris Kearns Goodwin as being very instructive on team building. Francois Nader referenced *The Goal: A Process of Ongoing Improvement* by Eliyahu Goldratt and Jeff Cox as being helpful when developing corporate values, vision, and mission statements. Hank McKinnell highlighted Ken Blanchard and Spencer Johnson's book, *The One Minute Manager,* as a useful model for managing people.

"But when it comes to leadership, what I found particularly helpful is to have a third party solicit anonymous feedback from your direct reports, and maybe even a step or two beyond that," says McKinnell. "It was through this mechanism that I was able to find out what I was doing as a leader that people particularly appreciated, as well as those things that weren't that helpful." McKinnell, like most CEOs, used to send out Christmas cards to about 200 people in the organization. He says this became known as the Christmas card experiment. During one year, he sent out custom-printed cards with a generic holiday message and signed each one. "The feedback I got was that this was very impersonal and I should probably stop doing it," he reveals. "I thought about this for a while and decided to take a different approach." The next year he again sent Christmas cards. But this time he wrote a personal message that was unique to each person. McKinnell described the feedback he received from those cards as being astronomical. "More people commented about my messages than I ever expected," he shares. From this McKinnell learned that some of the things he thought to be helpful not only weren't but were actually getting in the way. "But it isn't just learning what is and isn't working but being able to adjust course that is particularly important," he concludes.

Pyott suggests taking advantage of coaches. "Twelve years ago, we invited an executive trainer, Marshall Goldsmith, to conduct a presentation in the office. He had some very simple tools for improving team dynamics, and I will never forget those lessons on speaking up, not having hidden agendas, and thinking about how your behavior is impacting a colleague." Bonney adds to this by stating that coaches shouldn't be reserved for remedial work. "Coaching can help executives get to the next stage," he affirms. "Like many young CEOs, I was probably more willing to engage in conflict than most. But I didn't like having one-on-one conflict, as I didn't find I was very productive at it." To help, Bonney engaged Dianne Argyris, whose father (Chris Argyris) was the founder of the field of Organizational Behavior. "She helped me to develop the skills to have much more productive and less personalized conversations when conflict was inevitable," he shares. "I recommend her to many CEOs who find themselves in difficult interpersonal situations." Bonney says the nature of being a leader results in many difficult conversations, and therefore, one should spend a fair amount of time getting ever more effective at it.

Admittedly, attempting to combine the thoughts of these six industry icons into one concise article was a rather ambitious project. But there was a very good reason for doing so. Perhaps Hank McKinnell put it best when stating during the first few minutes of our interview, "I don't know of any other industry that does more good for more people than the biopharmaceutical industry."

CEOs 40 & UNDER

The Future of Pharma Innovation

CAMILLE MOJICA REY Contributing Writer

To take the pulse of the biopharma industry, *Life Science Leader* tracked down four CEOs age 40 and under. These are the people at the forefront of innovation — something that is no easy task in a heavily regulated, patient-centered industry. Biotech is not tech. Heading up a company that is developing a pharmaceutical is a lot more challenging and riskier than starting one in your garage that is developing the next mobile phone app. If the industry is to foster innovation, however, it must make it easier for risk-taking young people to lead the way. Listed below, in alphabetical order, are four of the industry's trailblazers.

37 Ken Horne
Symic Bio

Ken Horne assumed the role as CEO of Symic Bio in 2014. The Emeryville, CA-based company had been founded a year earlier to develop therapeutics targeting the noncellular component (extracellular matrix) of the body's tissues. These drugs are designed to inhibit pathological inflammatory responses and to affect matrix degradation and structure. Today the company has 34 employees. Two of its drugs, called matrix regulators, are currently in Phase 2a clinical trials, one for the treatment of peripheral artery disease and the other for osteoarthritis pain and disease modification. Horne is 37 years old and holds bachelor's and master's degrees in engineering from Stanford University. Before joining Symic Bio, Horne worked as a venture capitalist. He says he was drawn by the promise of the science to accept his current job as Symic's CEO and remains motivated by the potential to impact patients in a positive way.

31 Leen Kawas
M3 Biotechnology

Leen Kawas, 31, is CEO and president of Seattle-based M3 Biotechnology, which currently employs 10 people.

Kawas has a Ph.D. in pharmacology from Washington State University (WSU) and, after becoming CEO, participated in an executive business-training program at the University of Washington. A native of Jordan, Kawas says entrepreneurship was not a concept common in her culture. So, it came as a surprise in 2013 when WSU professor Joe Harding asked Kawas, then a postdoctoral fellow, to help start the company based on their research on treatments for Alzheimer's. Kawas was quickly promoted to CEO, deciding to learn the business of biotech by networking. A year later, she discovered she had connected with 719 people. Kawas says she now welcomes being outside her comfort zone, especially when she just might get to fulfill her childhood dream of curing disease.

40 Hamza Suria

AnaptysBio

Hamza Suria was named president and CEO of AnaptysBio in 2011, six years after the company was founded. AnaptysBio, which went public in January 2017 and has approximately 60 employees, is in the business of developing drugs for severe inflammatory disorders, such as atopic dermatitis, peanut allergy, and asthma. Suria, 40, has a master's degree in immunology from University of Western Ontario and an Executive MBA from the Richard Ivey School of Business. Suria says his focus has always been on the business end of biotech. He is motivated by the challenge of translating breakthrough science into value for patients and shareholders.

35 Ilia Tikhomirov

Formation Biologics

Ilia Tikhomirov, 35, is the president and CEO of Formation Biologics, which recently opened an office in Austin, TX, and employs 12 people. Tikhomirov immigrated to Canada as a teenager and went on to earn an undergraduate degree from the University of Toronto, as well as a master's degree in biotechnology and an MBA. Tikhomirov's attempt at earning a Ph.D. ended when he realized the project he had proposed had great commercial promise and that, if he didn't develop it himself, nobody else would. So, Tikhomirov started Formation Biologics in 2011. Today, Formation Biologics has closed multiple rounds of financing and has two drugs in development, one for the treatment of solid tumors, which recently started clinical trials, and one for the treatment of cancer and rare diseases, expected to start clinical trials in the beginning of 2018.

Life Science Leader turned to these young biotech entrepreneurs for insight on industry leadership, how to best foster innovation, and words of advice for those contemplating taking on the risk and rewards of running a start-up pharmaceutical company. Their answers have been edited for brevity and clarity.

LIFE SCIENCE LEADER: **Why did you decide to take on the job as CEO of your company?**

HORNE: Symic Bio approached the venture fund I was working for looking for both capital and a CEO. I realized I would rather be a CEO on the operating side rather than remaining on the investor side. The science was compelling enough to lure me away from life as a VC. I feel closer to helping patients in my day-to-day life than I did as an investor.

KAWAS: I was curious to see if I could do it, and, as it turns out, building a company is something that has suited me well. It is a job that needed to get done, so I decided to take it on. Business needs to focus on science and turn research into products that help people. When I was asked to help create an Alzheimer's drug, I did not think about what it meant to be a CEO or even what it meant to build a company. I was focused on the goal of creating the drug. Being a CEO and building a company were the tools needed to achieve the goal. I enjoy the challenges that come with the position and the responsibilities.

SURIA: My interest is in building value through the development of novel therapeutic drugs. With a team of motivated scientists and clinicians within the company, we will be able to advance the treatment of debilitating inflammatory diseases and create value for shareholders. Despite the challenges, I was excited about leading an organization that synthesizes the

scientific and commercial considerations in taking new drugs to clinical trials, and hopefully commercial launch in the future. My background is in immunology, drug development, and corporate finance. I saw the CEO role as a unique challenge that would allow me to synthesize the various strategic elements required in biotechnology and be part of a team that executes important medical advances.

TIKHOMIROV: I was young and stupid! And I wanted to bring my ideas to life. Actually, first of all, the company where I worked was very entrepreneurial and very open. The leadership exposed me to very different realms of drug development. They were talented people who readily shared their knowledge and expertise. This broad exposure gave me the confidence to start my own company. Second, in my family we have a tradition of entrepreneurship and social responsibility. If you can do something that could significantly affect people's lives, especially if no one else is doing it, it is your responsibility to take it on.

LSL: **What prepared you to take on this leadership role?**

HORNE: Most recently, I was at a venture fund. You are seeing more and more CEOs with my phenotype. Historically, CEOs moved from operating into investing. I find the reversal of that trend to be a good thing. It doesn't matter how smart you are. The lifeblood of a biotech company is private financing, so you need to be able to do it well. However, I am also fortunate enough to have had a CEO-like experience because I was the general manager of a portfolio company, running the company on behalf of my fund. It gave me confidence, and I learned the value in being able to draw upon a diversity of backgrounds within a company, especially when doing something no one has done before.

KAWAS: Being a pharmacist and having a scientific education is helping me significantly. When making business decisions, it helps to know the science and vice versa. Thankfully, I grew up learning how to make decisions. It's one of the hardest things about being a CEO. It's all about making decisions, and you don't get trained for that. My mom was a great role model for me. She ran one of the biggest hospitals in Jordan in a place that wasn't as progressive as Seattle. I learned from her that being an effective leader is all about putting in the time and being genuine with people. I also was lucky to have strong advisors early on who mentored me and shared with me their experiences, both successes and failures.

"It would be great to have a book aimed at scientists that outlines how to start a company and what it takes to be a really good leader."

Leen Kawas
CEO & President, M3 Biotechnology

SURIA: I grew up surrounded by educated professionals who built businesses through entrepreneurship. As I made my way through school, I realized that new scientific technologies — whether in medicine, electronics, software, or manufacturing — were transforming the way our society was organized and valued. It became clear that learning technical skills alone was no longer going to be sufficient to succeed in the 21st century. The ability to translate new technologies on a commercial level would become critical. So, my education straddled the scientific and business realities of medicine, and my pre-CEO work experience focused on understanding the strategic choices leaders make in a biotechnology environment to unlock the commercial value of medical breakthroughs. I was fortunate enough to work with, and receive mentorship from, smart scientists and clinicians who had previously made the transition from medical science to the business leadership positions. They became role models for my career.

TIKHOMIROV: It is easier to take risks when you are young. By the time people get all the basic scientific training and exposure they need to start on their own, they are usually in their 40s and have a family and responsibilities. It's not the best time to be taking big risks. It's one of the reasons we don't have as many companies started and run by founders in biotech as there are in the IT industry. I think times are changing, and more young people can get mentoring and broad exposure earlier in their careers. It's important that this trend continues.

LSL: **How could the biotech industry support more young leaders and entrepreneurs?**

HORNE: We need experienced people to step up and be mentors. I realized while I was in college that being the CEO of a life sciences company was my dream job. I sought out mentors and paid attention to what they did, what their career trajectories were, how you conduct yourself, and the need to be respectful of the people you want to lead. The most successful CEOs whom I had as mentors had a nonlinear path

and a diverse skillset. Seeing that factored into how I mapped out my career.

KAWAS: Despite my scientific training, I really wanted to understand the business concepts. So, I went to night school to study them. I was able to meet team members I am working with right now, but I think we need to officially train scientists in entrepreneurship in graduate school or have a separate program for scientists who want to be leaders in industry. It would be great to have a book aimed at scientists that outlines how to start a company and what it takes to be a really good leader. Maybe someone with experience reading this article will write that book. Conferences could focus on the entrepreneurship and the power of business to translate science.

SURIA: Leadership in any industry, particularly in biotech, is a multifaceted responsibility that requires entrepreneurs to navigate between technical and business considerations. I believe the biotech industry needs to create opportunities for its emerging talent to gain first-hand experience across disciplines and not become pigeon-holed into either purely becoming scientists or solely focusing on business. Every biotechnology CEO needs to articulate their drug development strategy in the context of the company's finance outlook and corporate development path. CEOs who cannot handle the cross-functional needs of their roles will be less suited for the challenges associated with financing the innovative medical opportunities of a biotech company. Our industry needs to foster education and mentorship to develop the next generation of cross-functional CEOs.

TIKHOMIROV: There should be an innovation path. The most important ingredient of that path would be the exposure of young people by their employers to all the areas of our industry. Too many people work in silos in large companies. They need to interact with people and real projects. The IT industry benefitted tremendously from young people getting involved, sharing their energy, and providing a new perspective. We should find a way to unlock the same potential in our sector.

LSL: **What advice would you give to other young leaders who want to start a company or take on a leadership role?**

HORNE: If you are wondering whether or not you should be a CEO, you shouldn't be a CEO. It is an extremely demanding job. It definitely shaves years off of your life. It is something that requires a lot of confidence. Some young CEOs surround themselves with people who don't know what they are doing. Naysayers are the most important people to have around, especially in biotech where most people are at least 10 years older. It's a heavily regulated industry, so experience is helpful. You have to find comfort in hiring someone who could probably take your job. That's what makes people in my position successful. Hire the best possible people that you can.

KAWAS: People need to realize that there is a significant amount of information that first year that entrepreneurs need to know. And to get that information, you have to talk to people. A lot of scientists don't feel comfortable networking, but it's critical to collaboration, meeting investors, and finding talent.

SURIA: You need to align yourself with strong, smart people who are not just mentors but also role models. Find a leader whom you respect and can use to model your growth, behavior, and strategic thinking. Learn what helps them be successful. For scientists, gaining experience in managing complex financial situations or business alliances is critical to going beyond your scientific education. If you have a business background, make it a priority to understand how drug development decisions are made and how scientists make sense out of emerging breakthrough biology. Fill in the gaps in your background such that you are able to go back and forth between drug development and business strategy.

TIKHOMIROV: First, from my own experience, there is a tremendous number of great ideas in our industry that never get developed. There is a lack of resources and people willing to take on these potentially breakthrough ideas that can help treat deadly diseases. If you see that kind of technology, you should take it on and develop it. But, you have to be passionate. Running a biotech company is tedious and complicated. If you care about what you are doing, it helps you to keep going. Second, be sure you surround yourself with very experienced people who have done this before. Third, even if you are not yet ready to start your own company, carefully watch our industry. Thirty to forty years ago you had to start a biotech company by building your own plant. There were huge up-front costs. Today, you can hire contract manufacturers to make and test drugs, as well as CROs to test them in human patients. The costs in biotech are still high, but they are only a fraction of what they were previously. Similar to IT industry in the twentieth century, this trend will continue and accelerate, which will create tremendous opportunities. As an industry, we are experiencing tectonic shifts.

Astellas Puts Oncology Front & Center

WAYNE KOBERSTEIN Executive Editor

DR. PETER SANDOR
Head of Oncology
Marketing Strategy, Astellas

DR. STEVEN BENNER
Head of Oncology, Astellas

Astellas has placed a big emphasis on oncology this year, pointing to its many assets, particularly in targeted therapies that are later stage, but also focusing through partnerships on immuno-oncology (IO). A conversation with Drs. Steven Benner, head of oncology, and Peter Sandor, head of oncology marketing strategy, follows.

WHY THE PRIMARY EMPHASIS ON ONCOLOGY? WHAT IS THE THINKING BEHIND THAT STRATEGY, BOTH NEAR-TERM AND FAR-TERM?

BENNER: Oncology is our largest therapeutic area and it's the area of our greatest investment right now. That's really because of the emerging clients and the opportunities to create important medicines for patients. Astellas has been in a number of other therapeutic areas based on its legacy companies, but for its future growth and the opportunity to create value for patients, oncology will be critical.

What we've done as a company is to try to build a broad portfolio of therapeutics for both hematology and solid tumors. We're looking for innovative science, and we're willing to do a variety of different kinds of deals or collaborations to obtain it, trying to find areas of excellence that we can bring into the company.

WHICH PRODUCTS AMONG YOUR ONCOLOGY ASSETS DO YOU NOW CONSIDER MOST IMPORTANT IN LEADING YOUR AREA STRATEGY?

BENNER: We have a combination in our pipeline of internal and external assets. Gilteritinib is in Phase 3 for AML that targets the tyrosine kinases FLT3 [FMS (McDonough feline sarcoma)-Like Tyrosine Kinase 3] mutation and AXL [from the Greek "anexelekto," uncontrolled]. That's an example of a drug that came out of our internal research at Tsukuba, Japan. We also have an antibody-drug conjugate (ADC) called enfortumab vedotin, which came from our fully owned subsidiary, Agensys, which was brought on as part of Astellas in order to allow us to be in the antibody space and to focus on antibody-drug conjugates. That's just reached proof-of-concept, showing single-agent responses in patients with liver metastases, previously exposed to checkpoint

inhibitors. That's a partnership codevelopment with Seattle Genetics, who had the original technology for the ADC. We completed an acquisition of Ganymed Pharmaceuticals [Note: German company] in December last year, giving us access to the biology around the claudin molecules and a lead antibody called IMAB362, which appeared to be very active against gastro-esophageal cancer in a presented Phase 2 study called FAST, which triggered our interest at Astellas.

WERE YOU ATTRACTED BY THE RESULTS IN GENERAL OR IN THE PARTICULAR INDICATION?

BENNER: Gastro-esophageal cancer is very difficult to treat — the outcomes are poor. To have a new therapy that, combined with chemotherapy, could significantly improve survival would be a very important advance. Based on expression of the target, IMAB362 is also a therapy being developed in pancreatic cancer. Ganymed also brought to us another earlier stage antibody, IMAB027, in development for ovarian cancer with a completed Phase 1 study. There are also research programs in earlier preclinical stages.

YOU SAID YOU WERE LOOKING AT ALL SORTS OF COLLABORATIONS TO BRING INNOVATIVE SCIENCE INTO THE COMPANY.

BENNER: We have a collaboration with MD Anderson around an antibody for treating AML and ongoing collaboration with Potenza Therapeutics in Cambridge focused on immuno-oncology. Through the Potenza collaboration, we'll be putting two IO drugs into the clinic this year. The second IND (investigational new drug) will be for a novel antibody that regulates T cells to change the response of the tumor microenvironment. With that program, we've already identified a lead for the third antibody, but that won't come into the clinic until after that.

YOUR CURRENT ONCOLOGY ASSETS ARE MAINLY MOLECULAR TARGETED DRUGS OR ANTIGEN-TARGETING ANTIBODIES. DO YOUR NEWER IMMUNO-ONCOLOGY ACQUISTIONS SIGNAL A RECOGNITION OF IO AS THE NEW LEADER IN CANCER THERAPY?

SANDOR: During the current period, while IO is still developing, we are still in a good position with technologies and assets that can deliver a very significant increment of benefit for patients and the healthcare system. Our product XTANDI (enzalutamide), introduced in 2012, is now used worldwide in treating prostate cancer. It has become the most frequently prescribed drug in the urology segment. Meanwhile, immuno-oncology has struggled to find an effective application in prostate cancer.

DESPITE THE PROBLEMS OF TARGETED THERAPY SUCH AS DRUG RESISTANCE AND TUMOR HETEROGENEITY, TARGETED DRUGS WILL BE ON THE FRONT LINES AT LEAST UNTIL IO CATCHES UP. BUT DO YOU SEE IO EVENTUALLY BEING THE STANDARD AND OTHER TYPES OF THERAPY SUPPORTING IT?

SANDOR: Not in prostate cancer, not in the near term. The T cell mechanism is definitely one that needs to be solved, but the long-term outlook is probably the same standard of care with some modifications and combinations within the same class. As we're thinking about our development for the agents that don't specifically work through an IO mechanism, there is a place, such as bladder cancer, where we know that enfortumab vedotin produces responses in patients who have been exposed to a checkpoint inhibitor — including patients with liver metastases, which is a very poor prognostic group. At the same time, especially as our own pipeline continues to mature, we're also thinking of combining our IO agents with other novel IO approaches.

CO-STIMULATION IS ONE OF THE PATHWAYS THAT YOU WANT TO EXPLOIT.

BENNER: Right. We have a variety of approaches at the basic research level, looking at emerging technologies. As we see how the field evolves, and our own internal capabilities and our collaborations evolve, we'll continue to pick areas that we want to focus on for a more in-depth kind of concentration.

The concept of the disease is very interesting right now because, typically for decades, really since cancer started being diagnosed and treated, we focused on the tumor, the organ of origin. Now we're increasingly characterizing these tumors, so we know our AML drug will be really important for patients with a FLT3 mutation. It is only a minority of those AML patients, but for them targeted therapy may be more effective.

Reshaping Astellas R&D

Sef Kurstjens, M.D., Ph.D., chief medical officer, heads pharma global development at Astellas. Here, Kurstjens gives a brief summary of the changes the company has made to the R&D organization and its current strategy.

KURSTJENS: About 2005 onwards, there was an express intention in Astellas to define our legacy. What do we want to be going forward? But we realized the research organization needed to continue evolving, so we embarked on a process of reshaping research, starting with the organizational structure. It had been a very line-driven organization, and we made it more therapeutic-area focused, thereby empowering the people deeper in the organization. The therapeutic-area focus actually provides a much better continuity of connection between research, development, and commercial through strategic teams.

Our second insight was, we were a great performer in immunology and urology, but we needed to continue to expand our focus. We subsequently decided to move into muscle disease, ophthalmology, vaccines, and regenerative medicine. We embraced the changes happening right now in new technologies, and we embraced open innovation. We put together the Astellas Innovation Management Group, which now has offices in Boston and San Francisco, because we want to partner with academia as well as biotechs. Our scientists in Japan have coined the phrase: "Best science, best place, best time."

Our therapeutic areas can be synergistic. Our deal with Cytokinetics gives us access to its fast skeletal muscle troponin activators, which have broad potential applicability in conditions such as COPD, general wasting, and cachexia in cancer. We look to apply technologies across different areas as appropriate.

Overall, we have focused on therapeutic areas, new modalities, and external innovation. We also know we need to maximize the value of the products we currently have – meaning, maximize their value for patients. We have our drug enzalutamide for prostate cancer, and as we expand its use to as many prostate cancer patients as is appropriate, we are driving it further, looking at other antigen-driven cancers. We also focus on productivity, and in the majority of cases, we will invest to determine whether we have value as quickly as possible because, sadly, this is a business of failure more than a business of success. At the same time, we're going to place some bets where we see the need is high, and the rationale is really good.

Ultimately, to characterize the individual patient's tumor from a genetic standpoint and then pick the most effective treatment combinations would make the most sense, and it will be a powerful way to use these therapies going forward. We'll increasingly see a trend toward more personalized medicine in cancer.

IS THAT THE DIRECTION YOU ARE TAKING WITH YOUR PARTNER PFIZER IN THE CONTINUED DEVELOPMENT OF XTANDI?

BENNER: Yes. Just in the past year, additional studies in prostate cancer were added to the label to better inform physicians about patients and about the characteristics of XTANDI. We have other studies going on in prostate cancer eventually to bring into earlier patient populations. We're also studying XTANDI with Pfizer in early stage and other prostate cancer subsets. We are looking every place where it makes sense scientifically to see whether there could be a benefit from the drug.

A BIG PHARMA PARTNER LIKE PFIZER PROBABLY ALSO HELPS YOU ANTICIPATE MARKET NEEDS AND DEMANDS AND ADJUST THE DRUG'S DEVELOPMENT ACCORDINGLY.

SANDER: We are equal partners in the United States,

and there is a continuous cooperation and exchange of experience between the two companies. We are producing the strongest strategies possible out of our combined teams.

WHAT ARE SOME OF THE KEY CHALLENGES IN PERSONALIZING CANCER TREATMENT, OUT IN THE REAL WORLD?

SANDER: It makes our job more complicated, in development and everything that follows. For a long time and until recently, oncology development and commercialization were relatively straightforward based on scientific knowledge of the drug candidates. Now there are many more products coming to the market. They are more complex. They may require physicians to select patients for particular treatments, often sequential regimens, based on disease biomarkers. Educational challenges are much higher, not only with physicians and providers, but even on the payers' side.

HOW DOES PERSONALIZED MEDICINE AFFECT THE CUSTOMARY PRACTICE OF OFF-LABEL PRESCRIBING IN ONCOLOGY?

BENNER: In the United States, oncologists have always prescribed off-label. We've also seen rapid uptake in the United States without promotion based on quality scientific publications or presentations. Regulatory agencies also have worked with us to bring new therapies forward with accelerated approval standards, surrogate endpoints, and many other mechanisms. It's important to remember, however, that Astellas only promotes its product for approved indications. Pricing and reimbursement issues will have an impact for some of these therapies.

PFIZER AND OTHER BIG PHARMAS HAVE TAKEN A LOT OF HEAT FOR POOR R&D PRODUCTIVITY IN THE PAST COUPLE OF DECADES; ARE SMALLER COMPANIES JUST BETTER SUITED FOR NEW-DRUG INNOVATION?

BENNER: What we've seen is that larger companies cannot sustain themselves and grow based solely on internal

research. Our internal research is productive — it has produced gilteritinib, it has produced enfortumab vedotin along with Seattle Genetics — and we believe it's important to have core capabilities internally in research. But the science is emerging pretty rapidly, and we're interested in a variety of different things, and it's just not feasible for a company to be in all the areas that require such expertise. We have used a variety of strategies to work with the best people, to gain access to the best science and most innovative approaches. Similar to our collaboration with MD Anderson, we have an earlier program at Dana Farber around the KRAS [Kirsten ras] oncogene. We're also working with other universities around the world, including Japan, to harness some of this great science that's coming out of academics. We're also working with startups like Potenza that are focused on producing antibodies in immuno-oncology — carefully defining what they want to do and focusing on that. Companies of that kind are often very productive, and by picking the most productive ones, we can develop an entire pipeline supplemented by our internal research. It will be necessary for us to be innovative in how we structure partnering deals, to continue to be competitive. Obviously, in the oncology space, there is now a tremendous amount of interest from basically every company with significant science.

SANDOR: This also goes beyond oncology; at Astellas, this is the corporate strategy. Putting these external innovation networks in place to supplement what we have internally was a conscious decision. It extends to partnerships with startups, academia, and other players in the field. It is part of the company's long-term innovation strategy.

IS ASTELLAS STILL A JAPANESE COMPANY?

BENNER: It's a global company based in Japan. They really did something pretty remarkable in the first place by creating Astellas through the merger of two legacy Japanese companies, one of which was over a century old. They did a successful integration and then decided to set up headquarters in Northbrook, outside of Chicago, to do global development. Many of our shareholders are outside of Japan now, and we also have aspirations to do global sales.

THAT IS QUITE A CHANGE – FROM THE TRADITIONAL TO THE GLOBAL STAGE – AND NOW PUTTING A RELATIVELY NEW ONCOLOGY FRANCHISE IN THE POSITION OF GROWTH LEADER.

BENNER: Neither of the legacy companies was focused on oncology, though they were tremendously strong in transplant and infectious disease. Medicinal chemistry was a great strength for both companies. After the merger, the company looked forward to the future, and two observations really catapulted oncology into the center: the explosion in the science itself and, more importantly for a developer, the ability to start translating some of those scientific observations into meaningful therapeutic approaches.

WOULD YOU SAY THE DIALOGUE BETWEEN COMPANIES AND ACADEMIA IS IMPROVING? IT HAS ALWAYS BEEN A BIT OF A CHALLENGE.

BENNER: I would say yes. Academic centers have become more focused and sophisticated in how they interact with industry. Industry has hopefully become more sensitive to where the development opportunities and needs are. It is hard for an academic researcher with great science and maybe preclinical models to take the next steps into human investigation and clinical trials, not the conduct but the regulation of them. That is where we can help. By identifying those synergies, where the academic science and our industry skills match precisely, we can do a better job of working together.

HOW CRITICAL IS MANUFACTURING FOR CLINICAL TRIALS AS A DEVELOPMENT SKILL?

BENNER: It is surely critical. With a small molecule, typically our chemists and our technology folks can produce as much as we need, and it's pretty cheap for them to do the manufacturing once the synthesis is well understood. But when we start moving into antibody therapies, the timelines obviously go way out, and the costs for the antibody are probably as great as total costs for all of the early clinical trials in first part of Phase 1. Now, with patient-specific therapies or cell-drug therapies, quality and manufacturing for clinical trials will become critical for companies to be successful.

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Drug/Device Development Changes Imminent: **21st Century Cures Act Becomes Law**

JIM SHEHAN AND DONNA HANRAHAN

Life sciences companies are navigating sweeping changes brought about by the 21st Century Cures Act (the "Cures Act" or the "Act") signed in December 2016. Of most interest to those companies is how the Act is changing the pathways and processes for developing and getting approval for new drugs and devices and new uses for existing products.

The drug and device provisions of the Cures Act are designed to accelerate the discovery, development, and delivery of life-saving therapies. While the rhetoric of the new administration has been largely confined to speeding up FDA review of approval applications, knowledgeable industry veterans are well aware that current review times are historically fast and that the real opportunities to speed innovation lie in the development and testing phases that occur prior to FDA review. The Act therefore incorporates the long-standing desire of patient advocacy groups, drug and device manufacturers, and research organizations to modernize the regulation of drug and device development and minimize barriers to innovation that occur prior to submission of an application. But don't expect most of these changes to occur soon — the Act allows the FDA several years to implement many of the most sweeping provisions and, on top of that, the FDA has a long tradition of missing deadlines set in legislation.

ADAPTIVE CLINICAL TRIAL DESIGNS

The Cures Act requires the FDA to hold a public meeting and then issue guidance on how drug companies can use complex adaptive and other novel clinical trial designs in the development of drugs. An adaptive clinical design uses prospectively planned modifications of one or more aspects of the study design based on analysis of interim data. Adaptive designs, which are already being used in the development of some products, may make studies more efficient (e.g., shorter duration), more likely to demonstrate a drug's effect, and/or more informative (e.g., by providing more dose-response information).

> *"Congress directs the FDA to make it easier for drug companies to win approval for new indications of previously approved drugs."*

The Act directs the FDA to issue a guidance that describes how such trials can satisfy the Federal Food, Drug, and Cosmetic Act's requirement of a showing of "substantial evidence" of safety and effectiveness and what information about such trials that companies should provide to the FDA. The FDA must hold a public meeting and gather input from stakeholders within 18 months of enactment, and then the agency must issue guidance within 18 months of the public meeting and finalize that guidance within one year after the comment period on the guidance closes.

GREATER USE OF PATIENT EXPERIENCE DATA IN APPROVALS

Expanding upon existing legislative mandates aimed at increasing the role of patients in the drug approval

process, the Cures Act requires the FDA to issue guidance on the use of patient data in the drug approval process. The agency is directed to explain how to collect patient experience data and what such data should consist of, how patient advocacy groups may propose draft guidance to the FDA, and how the FDA plans to use patient experience data when evaluating the risks and benefits of a new drug application in a structured risk-benefit assessment framework. Patient experience data includes data collected by patients, parents, caregivers, patient advocacy organizations, disease research foundations, medical researchers, and drug companies that is intended to facilitate the FDA's risk-benefit assessments. The Act gives the FDA five years to implement a patient-focused drug development guidance.

USE OF REAL-WORLD EVIDENCE AND QUALIFIED DATA SUMMARIES FOR NEW INDICATIONS

In two separate sections of the Cures Act, Congress directs the FDA to make it easier for drug companies to win approval for new indications of previously approved drugs. The first provision allows applicants to use "real-world evidence" to support approval of new indications. The Act defines real-world evidence as "data regarding the usage, or the potential benefits and risks of, a drug derived from sources other than randomized clinical trials." Implementation of real-world evidence has a particularly long and somewhat ambiguous deadline — the FDA is given six-and-a-half years to issue a final guidance or a "revised draft guidance."

The second change to new indications approval allows the FDA to rely upon "qualified data summaries" when approving supplemental applications. A qualified data summary is a summary of clinical data that demonstrates the safety and effectiveness of a drug for a "qualified indication," which is an indication that the FDA "determines to be appropriate for summary-level review." The Act does not require the FDA to issue guidance on the use of qualified data summaries, and this section of the law appears to take effect immediately.

PRIORITY REVIEW FOR BREAKTHROUGH DEVICES AND EASING DEVICE REGULATION

The Cures Act makes some significant changes to device regulation as well, the most significant of which is the establishment of a new breakthrough device pathway. Breakthrough devices are defined as offering "significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient

A large number of provisions in the 21st Century Cures Act are aimed at swift approval of new drugs and devices. About $430 billion is allocated over 10 years to allow the FDA to:

- Rely on data summaries and "real-world evidence" instead of the results of randomized clinical trials when weighing the approval of existing drugs for new uses.
- Use a "limited population" approval pathway for new antibiotics that would rely on a risk-benefit analysis weighing the needs of patients facing severe and untreatable infections against the possible harms to them.
- Expand its programs for expedited approval of breakthrough medical technologies for patients with life-threatening diseases that have limited treatment options.
- Modernize clinical trials and the means by which safety and efficacy data is accumulated and analyzed.
- Put patients at the heart of the regulatory review process.
- Support broader, more collaborative development, qualification, and utilization of biomarkers, which help assess how a therapy is working, and on whom, earlier in the process.
- Streamline regulations and provide more clarity and consistency for innovators developing health software and mobile medical apps, combination products, vaccines, and regenerative medicine therapies.
- Incentivize the development of drugs for pediatric diseases and medical countermeasures, and empower the agency to use flexible approaches in reviewing medical devices that represent breakthrough technologies.
- Use more funds to recruit and retain the best and brightest scientists, doctors, and engineers.

quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies." The FDA is expected to build on the existing priority review device pathway covered in a guidance issued April 13, 2015.

Other significant changes to device regulation include:

- the permitted use of centralized IRBs (institutional review boards) for device clinical trials
- a mandate that FDA consider the least burdensome appropriate means for demonstrating safety and effectiveness when reviewing premarket approval applications
- the designation of five categories of medical software that will not be regulated as medical devices
- a raised cap for humanitarian devices eligibility from 4,000 to 8,000 patients.

DRUG COMPANIES MUST PUBLICIZE THEIR EXPANDED ACCESS POLICIES

The Act makes a significant change to the regulation regarding the compassionate use of unapproved drugs outside of clinical trials. Companies that develop drugs for "serious diseases" must, within 60 days of enactment, post on a website their policies for expanded access, thereby making investigational drugs available to patients who are not in their clinical trials. These expanded-access policies must include procedures for making requests, the company's criteria for evaluating and responding to requests, and the length of time required to typically respond to a request. While less extensive than some proposals advocated by the right-to-try movement, this provision will require significant and immediate action by most drug companies.

STREAMLINING HUMAN SUBJECT RESEARCH REGULATIONS

The Cures Act simplifies human-subject and informed-consent research regulations. It requires harmonization of the HHS and FDA regulations within three years of enactment, directs the FDA to allow the use by researchers of joint or shared IRB review, and allows use of an independent IRB (institutional review board) or an IRB of an entity other than the sponsor of the research. Further, the Act provides additional opportunities for obtaining waivers of informed consent and allows medical device and drug trials posing "no more than minimal risk" to bypass the informed consent process if other safeguards are in place to protect the rights, safety, and welfare of patients.

MISCELLANEOUS PROVISIONS

The Cures Act contains a number of other provisions of significance to research-based life sciences companies. For example, it extends the pediatric priority review voucher program for drugs until Sept. 30, 2020. Another provision adds to the FDA's 2012 Drug Development Tools Qualification Program by establishing a review pathway at the FDA for biomarkers and other drug development tools that can be used to shorten drug development time and reduce the failure rate in drug development.

The Cures Act aims to speed the approval of drug-device combination products by clarifying how the "primary mode of action" of a product is to be determined and by requiring the FDA to meet with sponsors and agree early in development how best to study the combination product to meet approval standards. The Act also establishes procedures governing disagreements between sponsors and the FDA on how to treat a combination product.

In addition, the Act clarifies the FDA's authority over genetically targeted drugs by allowing sponsors to rely on data for the same or similar technology from previously approved applications by the same sponsor.

LOOKING FORWARD

The 21st Century Cures Act is rightfully regarded as landmark legislation. Although implementation will be slow, and it is not clear how the Act will be interpreted by the FDA and new FDA Commissioner Scott Gottlieb, it is clear we are in a new era of drug and device development. There will be challenges in navigating this brave new world that will require collaboration with legal counsel in order to take full advantage of opportunities and avoid pitfalls. L

JIM SHEHAN is head of Lowenstein Sandler's FDA Regulatory Practice.

DONNA HANRAHAN is a life science attorney at Lowenstein Sandler

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Automation Cuts Drug Development To 5 Years

GAIL DUTTON Contributing Writer @GailLdutton

Automation's advances and widespread integration into the scientific workflow can reduce drug R&D time from the usual 15 years to five, according to a study released by Frost & Sullivan. "Robotics already is meeting most relevant needs in drug discovery. Its impact in the coming few years will be remarkable," says Cecilia Van Cauwenberghe, associate fellow and industry analyst, TechVision at Frost & Sullivan. "Robotics will make pharmaceutical processes significantly more cost- and time-effective and allow precise, real-time documentation of every task. That, in turn, contributes to process optimization."

All of this happens by transferring mundane tasks to robots, thus freeing scientists for more creative and innovative work.

When automation first entered the pharmaceutical industry in the 1980s, it was seen as a way to improve precision and replace repetitive R&D tasks. With the emergence of high-throughput screening and the sequencing of the complete human genome in 2003, automated systems evolved to cope with increasingly complex tasks, such as large-scale DNA sequencing, single nucleotide polymorphism (SNP) analysis, and a number of variations and insert-deletions (INDEL) determination.

While some processes, including active ingredient development, haven't been widely automated, most of the needed gains will come from new and emerging advances in automation.

BACTEVO – 100 MILLION ASSAYS PER HOUR

Bactevo, a new drug development company formed to develop therapeutics targeting rare and untreatable diseases, has developed its own automation advancement. Its Totally Integrated Medicines Engine (TIME), announced in late April 2017, performs on-the-fly chemical synthesis and screens 100 million phenotypic assays per hour while simultaneously performing drug-dose response and ADMET assays. TIME may cut drug development time for Bactevo by at least five years.

"TIME was designed to work on minute amounts of reagents or single cells to enable ultrahigh-throughput screening on patient-derived samples, thereby bringing researchers closer to the disease they are working to cure," says Alex Alanine, Ph.D., COO. The approach is part of Bactevo's philosophy that lead generation and screening should be redesigned.

"By automating individual components of serial processes, pharmaceutical researchers inevitably removed themselves from the disease by increasing throughput, which led them further from the fundamental disease pathology," Alanine says. "High-throughput screening techniques tend to reduce a disease to its relationship with a single protein. That, however, probably doesn't reflect the true state of the disease. Most diseases can't be reduced to a single mechanism of action or cause of onset." Screening, therefore, should embrace the still-evolving system's biology approach. TIME enables that.

ASTRAZENECA AND NICOLA-B

In early 2017, AstraZeneca launched its drug discovery robot, NiCoLA-B, which is capable of screening 40 million compounds per year. "That's three times faster than previous high-throughput screening robots, at

half the size," Van Cauwenberghe points out. It even adjusts itself to the presence of people in the lab.

The NiCoLA-B robot will be deployed into the new AstraZeneca global R&D headquarters at the Cambridge biomedical campus where it will be shared with AstraZeneca's partners in the Open Innovation Initiative, Cancer Research U.K. and the Medical Research Council.

"The Open Innovation Initiative is designed to develop robots capable of replicating many of the simpler decisions made by scientists during experiments, thereby improving machine intelligence," Van Cauwenberghe elaborates. "The NiCoLA-B robot can be programmed to detect process imperfections in ongoing runs so it can take particular actions at the right moments."

BAYER'S MILLION-MOLECULE OCTOPUS

Automation also is crucial as tests continue to be miniaturized. "Microreaction mixtures involve many tasks that can be performed only by robots because humans lack the visual acuity and dexterity to carry out such experimental formats," Van Cauwenberghe says.

Bayer's Million-Molecule Octopus is a prime example. The mechanical device screens one million substances daily in Bayer's Wuppertal, Germany, facility. This ultrahigh-throughput system screens the pharmacokinetic and pharmacodynamics properties of chemical agents to find new, potentially disruptive therapeutic products. "The same workload would have taken an entire century using robots developed 20 years ago," Van Cauwenberghe says.

The benefit, aside from speed, is the ability of the Octopus to carry out completely new experimental designs. As she says, "It comprehends different combinable modules that can be integrated into the high-throughput system using new methods on demand. It also can be coupled with a second robot to optimize the preparation of the reactions, all harmonized through novel computer systems."

> *"Achieving such a dramatic reduction in drug-development time also requires a different way of conducting R&D."*
>
> **ALEX ALANINE, PH.D.**
> COO, Bactevo

The Million Molecule Octopus uses 1,536-well microtiter plates, testing substances first on isolated proteins and then on living cells using luminescence- or fluorescence-based measurement methods. A similar system is used in Bayer's Berlin lab. In Cologne, a robotic system is being set up to test and optimize the binding characteristics of more than 10,000 antibodies.

EMBRACE PARADIGM-SHIFTING OPPORTUNITIES

Using automation to reduce drug-development time requires more than merely automating some processes. Instead, Alanine says, "Achieving such a dramatic reduction in drug-development time also requires a different way of conducting R&D."

Drug-development companies need to complete the paradigm shift to direct-to-patient clinical recruitment using the internet and social media and to access real-time patient data from wearable clinical and consumer devices. "That will allow studies to form around a more focused set of patients, which should reduce the time frame considerably," Alanine says. Embracing more efficient participant recruitment and patient-monitoring strategies will transform the way clinical trials are run and could pare five years from the R&D timeline.

The final piece of the integrated automation picture calls for incorporating advanced analytics. "Without powerful analytics engines, it's impossible for humans to intelligently survey the vast quantities of data produced by ultrahigh-throughput screening to extract trends and patterns," Alanine says. Machine learning allows a faster and more precise science that reduces subjectivity in experiments.

CONVERGENCE IS LINKED TO AUTOMATION

Today's drug-development environment has been called a medical Renaissance. If the actuality lives up to predictions, that's because of the convergence of automated tools that speed up scientific advancements.

"The dramatic changes that laboratory automation has made during the past decade have revolutionized life sciences research and most especially drug discovery and testing procedures," Van Cauwenberghe says. As the convergence of other technologies (e.g., nanotechnology, materials science, electronics, synthetic biology, molecular self-assembly, high-resolution imaging, software development, and data analytics) accelerates, it becomes feasible to automate, miniaturize, and streamline drug-development processes to help them reach peak efficiency.

As that happens, scientists at all levels can devote more time to design and analysis and less to repetitive tasks, making the five-year drug development timeline Frost & Sullivan predicts feasible today.

Patient-Centricity — Answering Industry's Key Questions

ELIZABETH LINCOLN, M.A.

Patient-centricity is rapidly becoming the central theme of next-generation healthcare product development. Beginning in late 2015, DIA, in collaboration with the Tufts University Center for the Study of Drug Development (CSDD), initiated research we titled the Study of Patient-Centric Initiatives in Drug Development. The goal of this ongoing research is to quantify the benefit of engaging patients in all stages of healthcare product development. This article will share initial insights we have gleaned from our patient-centricity study.

The recent groundswell in industry's desire to move toward true and meaningful patient-centricity prompted DIA to explore quantifying the impact of patient engagement on healthcare product development. We had heard repeatedly from DIA stakeholders: "We want to be more patient-centric, but we just don't know how to do it, and we need evidence that it actually improves product development to get support to do it."

Our research study has been in progress for over 18 months and has provided a number of directional answers to both the "why" and "how" questions around moving toward true patient-centricity.

WHAT BENEFITS DOES PATIENT-CENTRICITY OFFER MY ORGANIZATION?

While the study uncovered dozens of metrics currently used by industry to assess impact, most are not uniformly defined or generally accepted across product development processes. However, we gathered enough data to show likely correlation between low-cost engagement initiatives and greater return on investment than high-tech and more expensive efforts. For example, data showed that clinical trial performance can improve when patients are engaged in protocol development.

Obviously, patient-centric processes allow industry to better understand patient needs, values, and priorities. Further, patient input better informs industry as they study benefit-risk preferences and then respond to those patient insights by providing better therapies to treat their disease or improve their quality of life.

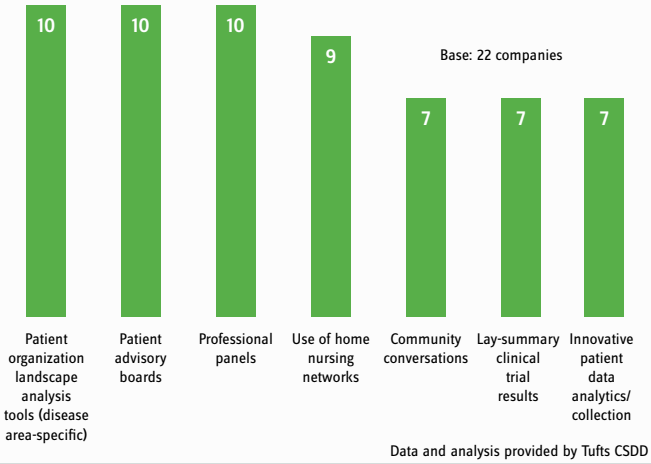
Patient-centric initiatives (PCIs) also open channels of communication between industry and patients that benefit both sides. For example, distribution of information to patients for safe and rational use of treatments is much easier when the path of communication has already been opened. PCIs may also make Patient Advocacy Organizations (PAOs) more aware of the challenges faced by industry in the healthcare product development process and give them a better understanding of industry's needs and how they can meet them.

WHAT KEY INITIATIVES STRUCTURED YOUR RESEARCH?

While the primary focus of the research was identifying and validating metrics that assess the impact — or return on engagement (ROE) — of patient-centricity, we knew that we needed additional information to support the adoption of patient-centric processes. The research, therefore, included gathering data on types of PCIs implemented, piloted, and planned to look for trends; characterizing management practices and organizational models to see if there are any correlations between internal structures and PCI implementation; and gathering guidance from regulators and frameworks from other sources that might address the

PATIENT-CENTRIC INITIATIVES: IMPLEMENTED

The most implemented initiatives were patient organization landscape analysis tools, patient advisory boards, and professional panels.



Data and analysis provided by Tufts CSDD

"how to" part of PCIs with the hope of providing some recommendations on standardizing processes.

What we found is that the adoption of patient-centric processes is still so new that no standards or best practices exist yet. However, those organizations that have ventured into PCI waters are learning by doing and capturing those learnings for future use.

WHAT ARE THE COMMON CHALLENGES EXPERIENCED BY COMPANIES IN STARTING PCIs?

Allocating resources/roles to support patient engagement is a challenge — especially given that patient-centricity is a completely new way for industry to interact with the people who are most directly impacted by their products. Not only do organizations not budget people or resources to support PCIs, but the individuals tasked with initiating PCIs often don't have the authority to ensure that these often revolutionary new processes are actually implemented.

There are many important challenges that must be addressed in defining how the organization will effectively interact with patients and PAOs across the product development life cycle, from developing clear guidelines around interactions and communication processes to addressing the real-life logistical barriers that patients must navigate when participating in a clinical trial. So, having dedicated resources to make this happen helps ensure the success of the PCI.

HOW CAN I PRACTICALLY APPLY ALL OF THIS?

There is no "one-size-fits-all" approach to patient-centricity. DIA realized this early in our research and early in our own experience engaging patients and their PAOs. We developed a tool to assess the different maturity levels and resources of PAOs in our Patient Advocacy Lifecycle Model (PALM). This general framework can also help industry understand the evolution patterns and needs of PAOs as they evolve from a start-up to one with the right resources and understanding of the healthcare product development life cycle to truly partner with them.

As part of the research project, DIA also assembled a Considerations Guide to Implementing Patient-Centric Initiatives in Healthcare Product Development as a more comprehensive tool that industry can use as they launch patient-centric initiatives. As companies answer the questions in the guide, they essentially design their own customized patient-centric program and processes.

The PALM and the considerations guide, along with insights coming out of the continuing DIA research study on measuring the impact of patient-centricity, can help jump-start organizations' efforts to become more patient-centric.

WHAT ARE COMPANIES SEEING AS THE GREATEST OPPORTUNITY IN PATIENT ENGAGEMENT WITH HEALTHCARE PRODUCT DEVELOPMENT?

After seeing patients as study subjects for so long, industry is now seeing patients and PAOs as partners who possess valuable insights and assets that can meet industry's needs to improve healthcare product development. Patients and PAOs are more educated and sophisticated than they've ever been. PAOs now offer scientific-quality disease-state data to industry and have become active partners — and in some cases drivers — in the development of new therapies. Therefore the biggest opportunity for companies may be in changing their attitudes and assumptions about what patients and PAOs are capable of doing and the impact they can have — and have already had — on innovations to treatment development.

Answers to these initial five questions will help get you started on the path to patient-centricity. Through effective PCIs, healthcare product value and access will improve, and industry will deliver innovative therapies to patients faster and in ways that have clearly considered their needs and concerns. In the next phase of the patient-centricity study, we will examine which models for patient engagement deliver the best and most valuable patient-centric results. L

ELIZABETH LINCOLN, M.A. is global director of engagement at DIA. In this role, she leads programs to build long-term engagement with patients and PAOs.

Precompetitive Partnerships **Skyrocket**

GAIL DUTTON Contributing Editor @GailLdutton

The number of precompetitive collaborations among pharmaceutical companies increased nine-fold between 2005 and 2014 when compared against the 1995 to 2005 period. Meanwhile, traditional partnerships merely doubled, according to "Partnering for Progress: How Collaborations are Fueling Biomedical Advances," a new study by Deloitte and PhRMA.

The popularity of precompetitive collaborations is due to their ability to share risks, streamline development, and educate patients in an environment in which the scientific, technical, and regulatory challenges are increasingly complex.

"Precompetitive collaborations often form in areas of research that are very difficult for a single company to pursue on its own," says Guy Seabrook, Ph.D., global lead, neuroscience external innovation at Johnson & Johnson Innovation. Such partnerships seek to expand understanding around one or more indications, therapeutic areas, or operational capabilities.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is one example. With more than 30 partners — many of which are life sciences companies — it formed in 2004 to enhance scientists' understanding of Alzheimer's disease. Since then, ADNI has developed methods for early detection, standardized clinical testing, and improved the efficiency of clinical trials for this disease.

"You can't do everything well yourself," Neil Lesser, principal, life sciences strategy at Deloitte, says. "Precompetitive collaborations let organizations access the best outside capabilities without the costs and complexity of bringing them inside as fixed infrastructure."

COLLABORATIONS PUSH NEW PARADIGMS

Precompetitive arrangements have also made a ton of progress in areas like advancing the understanding of diseases at the molecular level, public health, and clinical trial execution, which helped those companies develop their own programs. Deloitte reports that some precompetitive collaborations already are capitalizing on advances in those areas to develop new paradigms for conducting clinical research. For example:

- The Lung Master Protocol consortium is developing multidrug clinical trials for squamous cell carcinoma patients using genetic profiling. Success will further advance precision medicine.
- The Collaborative Novel-Novel Combination Therapies (CoNNCT) consortium is accelerating the identification of effective drug combinations that target cancer. Success will simplify testing, shorten studies, and reduce their cost while speeding the development of new treatments.
- The California Institute for Biomedical Research (Calibr) is advancing translational research in areas of unmet medical need by bringing together partners with deep understanding of the science, regulatory concerns, and development capabilities. Commercial partnerships may emerge.

Disease-focused areas will remain important in the future, but "the next wave of partnerships will focus on cutting the costs and cycle times for drug discovery, making drug development more patient-centric, and developing standards for evidence collected from real-world data sources. If you can leverage new sources of data in a way that is acceptable to global regulatory authorities, it can have a great impact on R&D produc-

tivity," Lesser says. Many pharmaceutical leaders are discussing the collaborative possibilities of integrating new data-collection methods and sources into pharmaceutical databases.

Those discussions may lead to precompetitive partnerships with IT companies to develop an industrywide infrastructure around informatics. Seabrook says, "This will be a rich area to think about."

TWO COMMON STRUCTURES

Joint ventures and consortia are the two most common structures for precompetitive agreements mentioned in the Deloitte study. Deloitte defines joint ventures as agreements in which at least two entities collaborate on R&D to reach a specific objective while sharing risks and rewards. They grew from 4 percent of all new pharmaceutical R&D partnerships in 2005 to 16 percent in 2014.

"Precompetitive collaborations can last many years, so organizations need a mechanism to redirect the research and a way for participants to exit if necessary."

GUY SEABROOK, PH.D.
Global Lead, Neuroscience External Innovation
Johnson & Johnson Innovation

Calibr is an example of a precompetitive joint venture. It was formed as a nonprofit by Merck in 2012 to translate lab discoveries into tangible patient outcomes. With heavy involvement from academic and nonprofit scientists, this partnership is unique in that it distributes profits from the sales or licensing of discoveries equally among participating scientists. Ongoing projects include advancing CAR-T cell therapies for cancer therapies and drug candidates for MS, cystic fibrosis, chronic obstructive disease, and tuberculosis.

Consortia, the other major type of precompetitive structure, involve more participants than joint ventures — at least three, but often 20 or more. Their formation peaked in 2011 when 62 precompetitive consortia were formed. They tend to have large goals that accelerate scientific discovery or industrywide development.

TransCelerate BioPharma Inc. is one example. It involves 18 biopharmaceutical companies, industry groups, and regulatory agencies in an effort to improve clinical standards. In addition to developing best practices for risk-based monitoring and comparator drug supply, it has created a centralized investigator platform.

The Deloitte study also lumps collaborations to provide financial resources or marketing, educational, and promotional programs into the precompetitive category. Projects to increase awareness of certain disease, like those of the Parkinson's Disease Education Consortium, are examples. This consortium was founded by the Michael J. Fox Foundation, seven pharmaceutical companies, and other stakeholders to educate patients and their families about Parkinson's disease.

SECRETS OF SUCCESSFUL PARTNERSHIPS

Simply forming or participating in a precompetitive collaboration doesn't ensure your goals will be met, of course. "For a transformative impact, senior-level sponsorship is imperative," Lesser says. These champions need to be actively involved, engaging and mentoring their representatives to the partnership to ensure the collaboration makes progress and remains on track.

Also, as the collaboration forms, establish governance and oversight, detail resource commitment, and clarify roles and responsibilities. "The best precompetitive collaboration teams are closely aligned at the outset about what they want to accomplish," Seabrook stresses. Outline the specific objectives and incentives for each individual partner. Understanding these points up front will help the collaborative team design the right milestones, structures, and incentives to help all participants meet their goals.

Track the direction of the consortia against its stated objectives, too. The mission may change as projects evolve, so participants need to be aware of any shifts and how those changes affect their own goals for participation. To do this, Janssen's neuroscience catalyst program includes milestones to help rein in any projects that may veer off-track. A Gantt chart depicting timelines for each activity within a project also helps, serving as both a project motivator and a productivity tool.

"It's not just the details of contracting that make a collaboration successful, but also the speed and focus," Seabrook says. "Precompetitive collaborations can last many years, so organizations need a mechanism to redirect the research and a way for participants to exit if necessary."

Precompetitive agreements are likely to continue to grow, both in terms of numbers of agreements and in their scope. Regulators and payers are demanding more evidence of efficacy that, increasingly, includes patient-reported information. Innovators are responding by gathering a wide range of stakeholders into precompetitive collaborations to provide the scientific, technological, and operational insights needed to develop innovative, efficacious drugs and deliver them to patients quickly and safely. L

How A Biotech Startup Networked Through The Valley Of Death

K. JOHN MORROW JR., PH.D. Contributing Writer

For young, emerging companies, the need for venture capital is acute, but even more so for biotech startups, which must negotiate the "Valley of Death" to reach profitability. This term describes the need for high levels of funding to move a promising drug concept through initial and costly clinical trials in order to gain acceptance from the investment community, a painful catch-22.

Cheng Liu knew nothing of these limitations when he envisioned his own biotech company. A Chinese émigré, Liu came to the University of California, Berkeley in 1990, obtaining a Ph.D. in biochemistry in 1996. He elected to do a postdoc at Chiron Corp., now Novartis Vaccines and Diagnostics, Inc., which eventually turned into a permanent position as a research scientist.

Then in 2005 he met Sandy Chau, a Chinese-American investor who has a background in chemistry and, as an angel investor, has played a prominent role in developing several companies. As a member of the billionaire investors club, Chau is well positioned to put money into new ideas as well as his pet philanthropic interests. He is the founder of Acorn Campus Ventures, an investment fund with its fingers in a number of Sino-American partnerships. The two soon found themselves to be kindred spirits. Chau, fascinated with biotechnology, asked Liu to provide a primer on the field. Although he had no background in the area, Chau proved to be a quick learner and eventually encouraged Liu to start his own company. "He said he would provide startup funds, but I would need to quit my job and devote all my energies to getting the company off the ground," recalls Liu.

So in 2006 Liu resigned from Novartis, and with a handshake and $2 million from Chau, he went off to start his own company — Eureka Therapeutics. "The idea that I might not succeed never occurred to me," Liu relates. The business concept was nebulous at first, based on the idea of using antibodies as anticancer therapeutics, but Liu pushed ahead. "At that time there were a lot of anticancer antibodies making the rounds, but they needed improvement, and we thought that we could do better."

A BAD TIME TO SEEK FUNDING

Backed by this bolus of funding, between 2006 and 2008 the company plowed ahead, moving the technology forward, which susequently led to additional funds being raised. With his small team, Liu pushed the concept of antibody dependent cell cytotoxicity (ADCC) as the company's weapon against cancer cells and succeeded in filing three patents on ADCC technology. These patents were developed with a staff of seven people in the same building in Emeryville, CA, that the company occupies today, albeit on a larger scale.

But in 2008 the money was running out. They had patents, but they needed more support. This was at the depths of the financial crisis, the worst of all possible times to be looking for financing.

With Chau's intervention, Liu went on to receive another $3 million in 2008 from Harbinger Ventures in Taiwan and Acorn Campus. That was good news, but the bad news was that they went for the next six years without any new infusions of cash. "At this point I decided we had to start producing something we could sell," Liu says. This entailed the production and licensing of antibodies for hire, a strategy that has brought in $15 million in revenue. "We also sold our antibody drug

> *"At this point I decided we had to start producing something we could sell."*
>
> **CHENG LIU, PH.D.**
> Founder & CEO
> Eureka Therapeutics

candidate to Novartis in 2014 for another $5 million. We did everything we could to survive."

PROVING THE NAYSAYERS WRONG

In 2010 Liu spoke at Memorial Sloan Kettering, where he met Dr. David Scheinberg, a staff member, and discussed treating cancer based on targeting cancer-related antigens inside the tumor cells. They initiated a joint venture partnership, which has since proven its worth. Collaborating with Scheinberg, Liu moved forward to establish a clinical focus to target the MHC complex, a critical component of the cell surface on nearly all cells of the body. Each MHC molecule displays a molecular fraction of its internal protein make-up, referred to as an epitope. The complexes behave as signals, alerting the T cells to the presence of foreign cells. "This was my 'eureka moment,'" Liu asserts. "In 2010 this was a crazy idea, to make antibodies against the antigen-MHC complex."

The Eureka strategy applied the CAR-T approach in which the antibody genes developed against specific cancer-cell antigens are inserted into a patient's T cells, generating a chimeric structure that targets, binds to, and destroys the T cell.

While initially there was great skepticism that the approach would work, the naysayers were proven wrong. With the science going apace, by 2014 the international investment picture had improved greatly, and Liu had a serendipitous encounter with another Chinese investor, Ce Yuan Venture, that decided to put $10 million into Liu's company, and Chau chipped in another $11 million.

More recently, in January of 2016 at a JP Morgan conference, Liu met with a representative of the Shanghai investment fund GP Capital Co Ltd., and after multiple meetings, raised another $20 million. Again, Chau and early investors put in another $25 million.

Today Liu is in a very strong financial position to push forward on his costly clinical trials. The company has been frugal in its expenditures, having spent $40 million since its inception. But it has raised a total of $70 million in venture capital (including additional funding from Chau) and another $20 million in sales of their antibodies and licensing their technology. So this leaves a total of $50 million in the bank.

Liu believes the quality of his data and the straightforward, no-nonsense fashion in which he presented it to potential investors were the critical factors that sealed the agreements. "I don't give sales talks," he emphasizes. "I am completely honest, and I simply present the data and let it speak for itself."

Liu stresses that his investors look to the long term, recognizing the agonizingly slow pace of drug development. "They are very patient and very passionate," he says. Now, paperwork has been submitted for Phase 1 trials at City of Hope Medical Center in Duarte, CA, expected to begin in January of 2018. These trials will evaluate a CAR-T immunotherapy with an alpha fetoprotein-MHC antibody against patients with liver cancer.

In the past 11 years of riding the biotech roller coaster, Liu's negotiation skills and knowledge of the language and culture of the Eastern Rim have brought him notable success, yet he knows he has not emerged from the Valley of Death. "When we look back upon our successes in discovery and fund-raising, it's easy to forget all the failures."

But Liu hasn't forgotten, and he is harsh when criticizing the failures he experienced while building his company. For example, his father died of pancreatic cancer in 2015, one of the same cancers for which Eureka is developing its treatment. "This is my greatest regret, that we were unable to move the developmental program more rapidly," he states. "In committing all my energies into pushing the program, it also compromised my marriage, which ended in divorce."

Now, as Eureka moves toward large-scale clinical trials, Liu recognizes that it must face the limits of its technology. "We have made the jump from preclinical testing in mice to patient trials. When you move into the clinic, the program is no longer under your own control. There are many external forces with which you have to contend: physicians, hospitals, the FDA, and manufacturing guidelines. So no matter how hard you work, you don't have control over the time line. That's our really big challenge." L

Personalizing The Work Of Life Sciences Organizations

BHASKAR SAMBASIVAN

Many parents can tell a story about the lengths they've gone to help their children when no doctor could provide an answer. But there's one story that stands out to me above the rest because it really drives home the vital need for data sharing, digital collaboration, and the establishment of a connected health ecosystem in the life sciences industry.

Essentially, it's the story of a family whose twin teenagers lead active lives today only because their parents worked tirelessly from their birth to understand the cause of their life-threatening ailments. In the end, the data did not come from medical specialists — despite countless tests and trips to the ER. The life-saving information came, in one instance, from a newspaper article they happened to stumble upon and, in another, from DNA testing that the parents themselves decided to undertake.

Their story, while inspiring, makes me wonder: Why should individuals with no background in medical research need to become pioneers on the data frontier to get the right healthcare treatment?

PERSONALIZING THE CARE CONNECTION

For the father in this story, who now works as a CIO at a life sciences organization, the mission of his industry is now a very personal matter, given his own struggles to obtain an accurate diagnosis for his kids. But it shouldn't take an experience like this to get life science leaders to embrace the industry's true value — beyond just producing pills — and how their organizations can better connect to consumers' lives.

- **First and foremost, let's start focusing on the data.** In the story above, it was readily available data — a newspaper article — that led to an accurate diagnosis. In an age when powerful AI-driven systems can churn through medical journals, expert findings, and other cutting-edge data in seconds, it may soon be considered medical malpractice not to use AI technologies to get to the real facts underlying patients' ailments. We are surrounded by constantly refreshed data and advanced ways to process that data — it will be hugely beneficial for life sciences organizations to harness this data in ways that benefit patients.
- **Accelerate the pace of ecosystem collaboration.** To unlock the value of data, new interplays are needed among the life sciences ecosystem — researchers, scientists, regulators, payers, healthcare providers, and patients — to more effectively mine and apply meaning from the new data flows to optimize processes long overdue for a digital refresh. Diagnostic, analyzable data rich with meaning is driving a connected future for healthcare, and life sciences companies have an important role to play as orchestrators of value. Platforms are set to grow around specific R&D processes and patient or clinician needs, providing mechanisms for open data exchange and intercompany innovation across the value chain. These platforms for innovation enable companies to connect, experiment, and collaborate to improve health outcomes.
- **Elevate the role of technology to executive levels in the organization.** Digital technologies can no longer take a backseat for life sciences organizations. From smart medical devices and intelligent pill bottles, to wearable bio-sensors and digestible microchips — digital is supercharging innovation and opportunity across the industry. In our recent research, life science professionals realize this, with 84 percent citing Big Data/analytics as critical talent capabilities for 2020. It's time for organizations to stop seeing IT as a cost center and as a strategy driver.

It's clear that the industry is shifting its focus to delivering care, not drugs. It's now time to inject the work of life sciences with a personal motivation to harness data and digital approaches to driving the best care for patients.

BHASKAR SAMBASIVAN is SVP and global markets leader at Cognizant Life Sciences.

5 Areas To Focus On To Improve Drug Development Productivity

DAN PATRICK

Much has been written about opportunities for improving the drug development process. Although there are many areas ripe for process improvements, let's focus on the following five:

1. R&D PORTFOLIO PRIORITIZATION

A key first step is ensuring R&D projects are aligned to the strategic goals of the company. For smaller biotechs, there will likely be time and cost pressure due to a limited "runway" of available funding as well as intense pressure to monitor the burn rate of spend. This step also can eliminate extraneous projects and bring sharper focus to the allocation of your R&D resources.

2. CLINICAL STUDY PROTOCOL DESIGN AND PROTOCOL AMENDMENTS

It pays to build in quality up front at this stage. Taking the time to craft a clear, well-written, and detailed clinical study protocol will help save the company valuable time and money by reducing the number of amendments or changes to the protocol as the study progresses. For every material amendment to the protocol, the company will spend time rewriting the document as well as communicating the changes to internal staff and clinical study investigators. If using a CRO, they will likely charge a substantial fee for each amendment.

3. ACCURATE PLANNING OF STUDY STARTUP

Many new clinical studies are scheduled to commence in the first quarter of the year. This creates the potential for resource bottlenecking. If the volume of projects in the R&D portfolio is sizable relative to the company's pool of resources, the caution is not to be too optimistic about the firm's ability to execute the full slate of new studies in such a short time frame. Also, remember that clinical study investigators and CROs are likely being inundated by similar requests from other pharma/biotech firms to kick off studies early in the year. On the flip-side, there is a significant cost associated with holding internal resources, such as clinical monitors and clinical supplies, in queue waiting for a study to start. Minimizing this wait time by staggering study starts throughout the year enables investigator kick-off meetings and study-planning activities to be more tightly coordinated for more efficient and productive study startup across the R&D portfolio.

4. STUDY OVERENROLLMENT

Clinical statisticians ensure a study is "powered" to achieve the statistical significance required for data-set analysis and FDA filing. While the clinical study team may deliberately choose to overenroll patients in the study as an extra measure to ensure greater statistical significance, close monitoring and frequent updates of patient recruitment and enrollment can help ensure the study does not have unnecessary overrun. Costs for overenrollment can be very large when considering the investment in additional drug supply as well as site monitoring — not to mention the delay it causes in getting the new drug to market.

5. DISCIPLINED GO/NO-GO DECISIONS

Having a clearly defined and documented set of project evaluation criteria is essential to make the critical go/no-go decisions as an R&D asset moves through the pipeline. Examples of such criteria may include:

- NPV (net present value) analysis for the project life, highlighting key assumptions and primary drivers of value
- sensitivity analysis on sales, operating expenses, number of patients under treatment
- scientific merits of the study, including objective opinions from KOLs, if required
- demonstrated alignment with the company's strategy.

Adhering to an objective set of criteria with which to evaluate R&D projects also will permit decision makers to remove emotion from the decision-making process and simplify communication of portfolio decisions to various internal stakeholders within the organization.

DAN PATRICK is a senior consultant at TayganPoint Consulting Group.

How To Attract & Lead Top Talent

JOHN SPENCE

JOHN SPENCE is one of the top 100 business thought leaders in America and top 500 leadership development experts in the world. You can find out more about him at JohnSpence.com

Recently I did a study of more than 10,000 high-potential employees at leading companies around the world. The people I interviewed were the best of the best, the sort of employees that any organization would love to have on their team. I call this type of person a "voluntary employee," because they are so good at what they do that if they quit their job at 9 in the morning they would have a job at the competition by noon. Which means they work at a certain company because they want to, not because they have to.

SO, I ASKED THEM THIS QUESTION: "WHY DO YOU WORK WHERE YOU WORK?" HERE IS WHAT THEY TOLD ME.

1. Fair pay, which they defined as 10 percent above or below what they would make to do the same job anyplace else.
2. Meaningful/challenging work. It was important to feel like they were using all their skills and talents to do something important.
3. Cool colleagues. It's straightforward; A-players only want to play on a team with other A-players.
4. Winning culture. They want to work in a company with a fun, supportive, and enjoyable environment.
5. Personal and professional growth. They want their employer to invest in their continual growth and improvement, and they want a clear career path to move up in the organization.
6. And the most important element: They want to work for a leader they respect and admire.

WHICH LED ME TO MY NEXT QUESTION: "WHAT ARE THE CHARACTERISTICS OF A LEADER YOU WOULD WILLINGLY FOLLOW?"

1. Honesty. More than 90 percent of the respondents listed this as the single most important thing they look for in their leader.
2. Competence. An effective leader needs to be highly competent at their job and in their leadership skills.
3. Courage. They expect a great leader to make tough decisions and take bold risks, but what they wanted was a leader who was courageous enough to admit they didn't have all the answers. Another word they used here was "Authentic."
4. Communication skills. The two skills they said were most important were asking great questions and being an intense listener.
5. Team player. They wanted a leader who would treat them as a partner and peer, not just an employee.
6. Empathy. A leader who realized that they had a life outside of the company that was as, or more important than, their job.

I believe that the lists above outline what it takes to attract, retain, and lead the very best people in your industry. L

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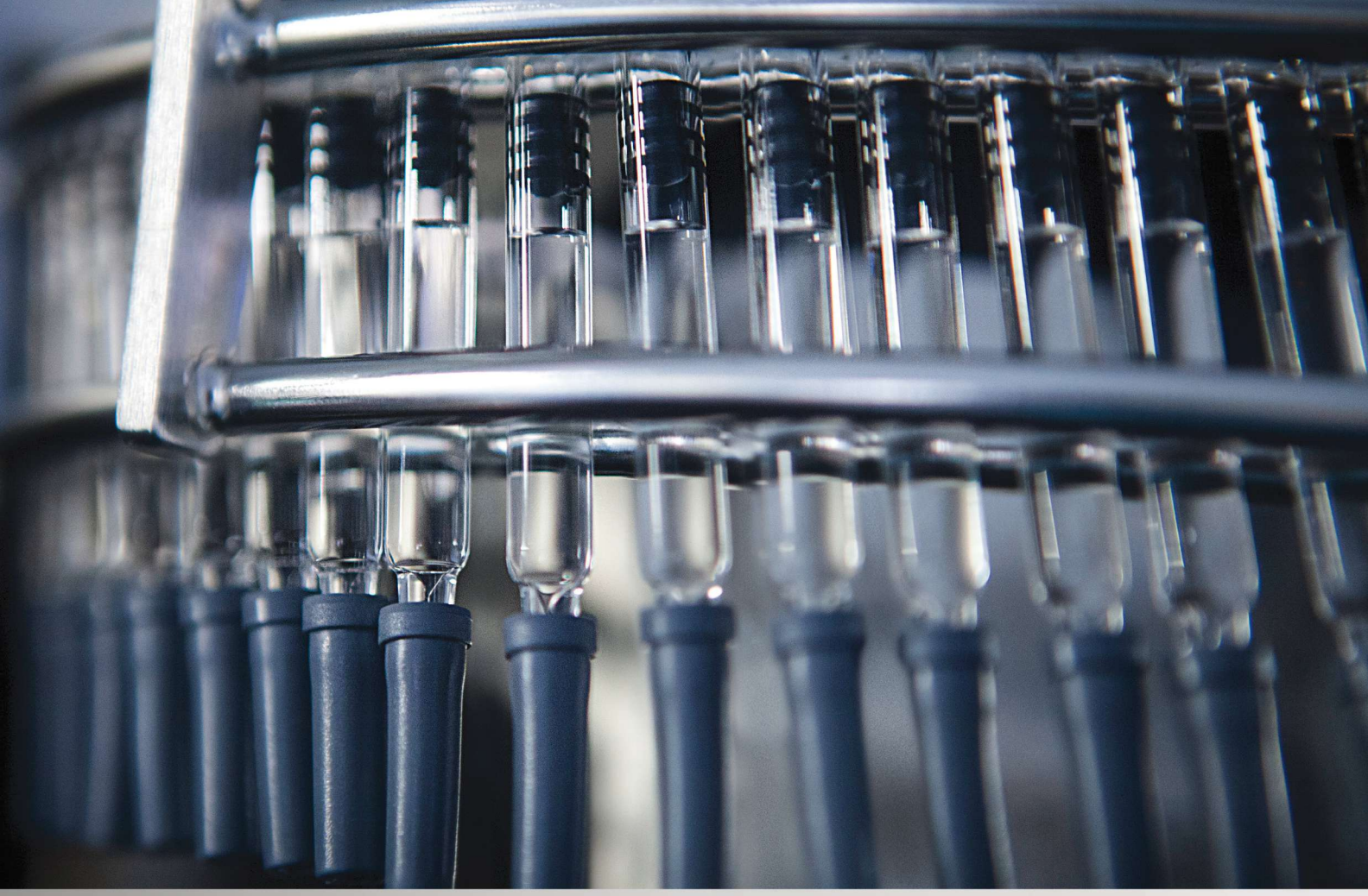

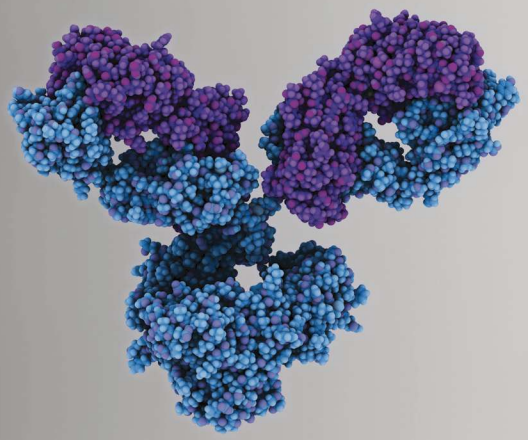

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