Life Science Leader

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NOVEMBER 2017

SOPHIE KORNOWSKI-BONNET, PH.D.
Head of Partnering, Roche

What Makes Roche's Approach To Partnering Unusual

p. 16

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

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

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

Reduce Unnecessary Transfusions

in low blood-loss surgery:

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

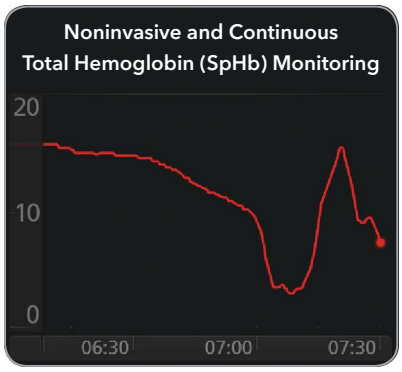
in high blood-loss surgery:

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

Initiate Timely Transfusion When Transfusions Are Needed

in high blood-loss surgery:

> Transfused an average of 41 minutes sooner[2]



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[1] Ehrenfeld et al. *J Blood Disorders Transf.* 2014. 5:9. [2] Awada WN et al. *J Clin Monit Comput.* DOI 10.1007/s10877-015-9660-4.

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

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

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

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- Plan for measures to mitigate risk
- Expect the unexpected with a back-up plan

Step 2
Define

- Consider the logistics: Decommissioning… Packing… Unpacking… Transporting… Hazmat Handling… Recommissioning… IT Connections… Temperature Control… Global Regulatory Compliance…

Step 3
Communicate

- Determine who needs to be in-the-know. From lab managers to business leaders and supply vendors to facility managers and general company employees – **an internal and external communications plan is crucial to the success of a laboratory relocation**

Keep an eye on lead time – determine what needs to be planned for in advance like "Goods in Transit" insurance, regulatory documents that need to be processed, time-sensitive and temperature controlled projects.

Step 4
Contingency Plan

- Plan for multiple scenarios even the worst case scenario so your team is prepared with a contingency plan
- Know your partners, providers and outside vendors and their policies and if there is room for flexibility

Contingency planning should include a RAID — Risks, Assumptions, Issues, and Dependencies — or Risk Register. Created at the start of the project and updated daily, the RAID lists any potential risk or issues, which are "opened" if they occur and tracked throughout the project until resolved.

Step 5
Partner

- Choose a single solution provider with proven experience

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Life Science Leader

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Why Semantics Matter In Pharma

ROB WRIGHT Chief Editor

As children, we were all taught the phrase, "Sticks and stones may break my bones, but words will never hurt me." But as adults, we all know that words can hurt and, more importantly, that semantics do matter. I was reminded of the latter on two occasions recently.

The first time was when I purchased a book that I had heard a lot about but hadn't made time to read — Atul Gawande's *Being Mortal*. I was only 58 pages in when I had an epiphany that caused me to scrawl some notes about patient-centricity in the margin.

Gawande was writing about Felix Silverstone, M.D., a geriatrician whose life's work had focused on the management of aging. At age 82 he had to retire to care for his wife, Bella, whose health was in decline. The couple moved to a retirement community and made out pretty well for a while. But as Felix entered his 90s and Bella's care became more than he was capable of handling, she was soon moved to the nursing home floor. Although only one floor away from their apartment, the move proved significant — and not for the better. Silverstone and his wife soon found the efforts of the ever-present nursing home staff to be exasperating. "Some tended to Bella more as a patient than as a person," Gawande wrote. And that was when it hit me. Do patients want to be treated as patients, or do they want to be treated as a person? I argue for the latter and believe companies that have been overly focused on becoming patient-centric and institutions that have shunned the term "personalized medicine" in favor of "precision medicine" have missed the boat — semantically speaking. Because being labelled as a patient signifies something being amiss. And while a person most likely wants the delivery of their care to be as precise as possible, doing so in a manner that fails to address their needs as a human being just doesn't sound all that patient-centric to me.

I was reminded again about the issue of semantics when I was researching my story (p. 16) on Sophie Kornowski-Bonnet, head of Roche partnering. As far as I can tell, she's the only executive leadership team member of a top 10 Big Biopharma with a title that includes the word "partnering." I found that surprising since partnering seems to be one of the most popular business strategies in biopharma today. In fact, not one of the top 10 best-selling drugs for 2016 was developed by the company now benefitting from its sales; they all came from a partner company. Now to be fair, Sanofi and Amgen each have executives with responsibilities for "business development," but semantically speaking, that term doesn't connote the same feeling as partnering. I'm guessing that as companies become more reliant on external innovation to fill their pipelines, the ones that will succeed may be those that put more emphasis on the partnering function.

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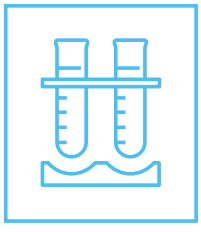

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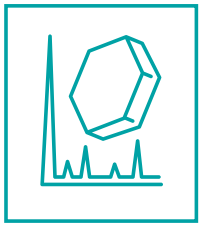

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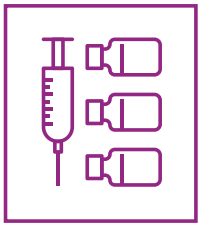

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EAB

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Q What are you working on outside of your role as plant manager for MSD Pharmaceutical Operations at Merck?

A AS AN ACTIVE MEMBER OF MEXICO'S CANIFARMA (National Chamber of the Pharmaceutical Industry), I've been presiding over its Operations & Manufacturing Commission for the last three years. This is a diverse group of pharma executives, representing both national and multinational companies, with an ambitious agenda of positioning our pharma industry as a priority endeavor for the Mexican government. The potential impact could include enhanced incentives and benefits for our industry, emphasis on R&D activities, and a more secure supply chain through the development of world-class, highly compliant local sources of supply. With a highly respected and progressive regulatory environment and a technically skilled workforce, these efforts will continue to provide Mexico with the tools to become a prominent member of the world's pharma community.

RAUL DIAZ
is plant manager for MSD Pharmaceutical Operations at Merck and directs the Merck Manufacturing Division's (MMD) human health operations in Mexico. For the last 26 years, he has managed MMD facilities in Europe and the U.S., and led global strategy development and execution activities.

Q What is your approach to balancing your dual responsibilities of serving as chief medical officer and coleader of the Medicines Development Unit (MDU)?

A BALANCING THESE RESPONSIBILITIES depends greatly on what the immediate business needs are. For example, earlier this year, I was primarily engaged in organizational change. Now, I'm deep into 2018 business planning. One notable difference in the two facets of my role is that I'm usually more in control of change in the MDU work. But when it comes to external medical affairs activities, change often is dictated by the external environment, the healthcare environment, or the political or legislative environment. I have less ability to manage the timing and nature of certain activities.

TIMOTHY GARNETT, M.D.
is chief medical officer and senior VP of the Medicines Development Unit at Eli Lilly.

Q What is your opinion on the FDA´s new approach to approving drugs based on their genetic profiles?

A THE FDA'S RECENT APPROVAL of Merck's pembrolizumab (Keytruda) represents the next generation of regulatory advancements in policy recognizing the importance of specific biomarkers rather than the tumor's location in the body. It is important to point out that the FDA and the biopharmaceutical industry have been moving in this direction over several years, particularly in the area of oncology where more than 20 percent of the NMEs (new molecular entities) approved by the FDA (over the last three years) have had a personalized medicine approach. The importance of "pathway" over "tumor location" will impact the entire healthcare ecosystem: all stakeholders will need to evolve to a more personalized approach to ensure access to these new ground-breaking medications for the hope of better outcomes for all patients.

JOHN HUBBARD, PH.D.
is a board member of Agile Therapeutics and has over three decades of experience including executive level positions with Pfizer, ICON, PAREXEL, and Hoechst Marion Roussel Pharmaceuticals.

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Commenting on the CEO Corner article "Successfully Transforming An Organization: An Active Approach":

"Excellent article! It is exactly what I have experienced through multiple big transformation deals. It seems a lot of time companies are focusing on meeting the synergies' target by cutting across the functions. Also, for each transformation there will be hidden costs, such as penalties for stopping contracts, expenses involved for technology alignment, as well as how non-GAAP items will impact cash flow."

D., (PREFERS COMPANY NAME REMAIN ANONYMOUS)

Dear Rob,

In response to your August 2017 column "Has Your Company Ever Been Held For Ransom?":

One of our scientists clicked on a spoofed email message, which resulted in every file on our file server being irreversibly encrypted. Attempting to open any file (MSWord, Excel, PowerPoint, etc.) generated a message indicating that only for a fee could the file be unencrypted, and that trying to decrypt the file would result in its permanent destruction.

The ransom requests were traced to a Russian IP address, and we had the concerns that you describe with respect to there being no guarantee that paying a ransom would result in any (not to mention all) files being decrypted. So, we deleted all files from the server and restored them from the previous night's backup copy. Fortunately, the backup (which is automatically performed every night) was not corrupted and, with the exception of a few hours' work, no files were lost and no ransom was paid.

There are at least two lessons to be learned from this experience: 1) Check for actual sender addresses before clicking on any incoming email messages, and 2) Be certain that full data backups are being executed at frequent intervals. I hope your readers will benefit from reading about our experience.

M., MOUNTAIN VIEW PHARMACEUTICALS

Rob,

It's going to be very challenging for you to beat that July issue. The retired CEO wisdom was great, as was the article on the young CEOs. That summary on the 21st Century Cures Act was excellent, too. You guys are a step above. I always find something to stimulate thought.

P., PHLEBOTICS

Bravo on your article and keep up the good work ... days are already long enough, and avoiding the level of negative chatter that exists in the general media today is a welcome change.

S., MAETRICS

In response to the blog, "My Top 10 Quotes From David Hung, Axovant Sciences CEO":

I worked for David, and there is nobody better at leading people from top to bottom.

BRIAN

To editorial board member Leslie Williams regarding her recent Ask The Board Q&A:

Leslie,

I wanted to let you know that I loved your biotech advice piece in *Life Science Leader*. It was great! As the CEO of a small biotech, I could not agree more. Helix Biomedix is a peptide-based (dermatology-focused) company. It's a small world and an even smaller world of women CEOs, so congratulations on all your hard work.

R., HELIX BIOMEDIX, INC.

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Republican Dysfunction Could Result **In Radical Democratic Health Agenda**

JOHN MCMANUS The McManus Group

The Republican Party's dysfunction in handling healthcare issues has dominated the news for the entire Trump presidency. Now many political analysts believe the Republican base's frustration with the inability of the party to repeal Obamacare, despite controlling both chambers of Congress and the White House, makes a Democratic takeover of Congress in 2018 a real possibility. Midterm elections are low-turnout affairs, and the side that is most energized generally wins. Plus, the president's party almost always loses a substantial number of seats in midterms.

An examination of Democratic health priorities is therefore in order.

Last Congress, Senator Bernie Sanders (I-VT) introduced his single payer "Medicare for All" legislation without a single cosponsor. A few weeks ago with great fanfare, he rolled out the identical legislation with 16 Democratic cosponsors, including the leading presidential contenders for 2020 — Elizabeth Warren (D-MA), Kristen Gillibrand (D-NY), Kamala Harris (D-CA), and Cory Booker (D-NJ) — who apparently believe support for this leftist legislation is necessary to demonstrate their bona fides to the Democratic base. A companion House bill now has 120 Democratic cosponsors, more than half of the Democratic caucus.

Oh, what a difference a year makes! As liberal *Washington Post* columnist Dana Milbank observed, "The Democrats Have Become Socialists!" How so? The bill:

- requires every American — other than those enrolled in the Veterans Administration and Indian Health Service programs (stellar programs, you know) — to enroll in the government-run Medicare program.
- requires all healthcare providers to sign participation agreements.
- prohibits employer coverage or individual purchase of insurance for benefits provided by Medicare.
- requires the Secretary of Health and Human Services to negotiate the price of prescription drugs and establish a national formulary.
- eliminates out-of-pocket spending on all healthcare items and services, except for *copays on brand-name drugs* to encourage generic utilization. (You can't make this up.)

Radical stuff! How would it be financed? The bill does not specify the mind-boggling funding necessary to feed this beast, but Senator Sanders later issued a white paper delineating a series of "options" including:

- 7.9 percent payroll tax on employers
- 4 percent income tax on all individuals
- substantial tax hikes on individuals making more than $250,000 with a top marginal income tax rate of 52 percent, a new "wealth tax," increases to the estate tax, limitations on deductions, and hikes on capital gains
- nearly $1 trillion in new corporate taxes

These job-killing and confiscatory tax hikes are still likely to fall well short of the full cost of the program.

Emory University Professor Kenneth Thorpe, a well-known, centrist health economist, estimates the program to cost an average of $2.5 trillion a year, creating a financing shortfall of $1 trillion annually.

Sanders' home state of Vermont scrapped its single payer plan before it even went into effect because of the inability to control costs. The Vermont law would have required an 11.5 percent payroll tax on businesses, plus an additional state income tax of up to 9.5 percent. The plan would have covered about 94 percent of Vermonters' healthcare costs on average, not including adult vision or dental coverage. But Democratic Governor Peter Shumlin pulled the plug, citing the inability to control costs and calling it the biggest disappointment of his career.

"Some experts believe about one-quarter of priority-reviewed drugs could be impacted by the NIH fully exercising its march-in rights."

Of course, government cannot control demand for healthcare services. It can only control the supply by deciding who gets what, when, and how. It does so through a raft of regulations, fee schedules, and administered prices. If resources cannot adequately meet demand, rationing of care is likely where patients are delayed or denied access to certain items or procedures that are in high demand. And that is precisely why such proposals must be defeated.

It is easy to dismiss single payer as a pipe dream. But let's not forget that Senator Sanders — an avowed socialist — nearly won the Democratic nomination against the most famous, well-connected, and credentialed woman in the world. President Trump's takeover of the Republican Party from mainstream, market-focused Republicans has shrouded the radical changes that have simultaneously transformed the Democratic Party.

The slow-rolling collapse of Obamacare has not made Democrats rethink that top-down, government-focused approach to healthcare. Rather, it reinforces the emerging consensus of their progressive base: Even more government control is needed because Obamacare relied too much on the private sector (read: heavily subsidized and regulated insurance companies). Government must literally control the entire healthcare system — comprising nearly one-sixth of the economy.

MARCH-IN RIGHTS

If this is not enough to make you yearn for the centrism of Barack Obama, then an examination of Democrats' latest fixation on pharmaceutical policy may. Last year, 51 Democratic lawmakers led by Rep. Lloyd Doggett (D-TX) signed a letter calling on the NIH to issue guidance on when "march-in rights" could be used to bypass patents on drugs developed, at least in part, with federal funding.

The issue emanates from the 1980 Bayh-Dole Act, which was meant to give universities, small businesses, and nonprofits ownership of patents for inventions derived from federal funding. However, that law also includes a clause known as march-in rights to permit federal agencies to license a patent when "action is necessary to alleviate health and safety needs which are not being reasonably satisfied or available to the public on reasonable terms." It has never been enforced in its 37 years.

The NIH has not issued guidance on when march-in rights would apply and denied all six petitions requesting it to exercise those rights. A common theme in the denial of those petitions was that concerns over drug pricing were not, in and of themselves, sufficient to provoke march-in rights. But the threat could be substantial. Some experts believe about one-quarter of priority-reviewed drugs could be impacted by the NIH fully exercising its march-in rights.

The Doggett et al. letter argues that the NIH must take a more aggressive approach to enforcing the law to combat high drug prices because many drugs "are not available to the public on reasonable terms." The letter contends that simply issuing strong guidance would "reduce the need for having to actually exercise march-in rights and permit pharmaceutical companies to make more informed pricing decisions." Informed of potentially losing patent protection based on a pricing decision may change behavior? Why, yes!

Congress could, of course, amend the statute to provide greater clarity and guidance on the circumstances when march-in rights could be applied. Rep. Doggett stands to become the chairman of the Ways and Means Health Subcommittee should the Democrats take control of the House of Representatives. 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.

Abivax

Pushing to cure HIV infection – by clearing the virus from the body

WAYNE KOBERSTEIN Executive Editor
@WayneKoberstein

SNAPSHOT

Abivax is in Phase 2 clinical development of its lead drug candidate, coded ABX464, as a potential functional cure for HIV infection, based on evidence that it clears the virus from the body. Earlier candidates in the Abivax pipeline, discovered and developed using similar scientific insights and platforms as with ABX464, offer possible treatments for dengue fever, RSV (respiratory syncytial virus), influenza, and other viral diseases. A related branch of research with ABX464 has spawned an early clinical program in inflammatory bowel disease (IBD).

WHAT'S AT STAKE

The first thing to know about Abivax is that it is not a vaccine company. Changes since its 2013 founding in France turned the company's focus from prevention to cure. Its lead drug, coded ABX464, may reduce viral reservoirs of HIV in the body to vanishingly small levels and keep them there, effectively rendering patients completely free of disease. The company has made the ongoing and future Phase 2 trials its top priority for some time to come.

CEO Hartmut Ehrlich, M.D., joined the company as a veteran in building R&D portfolios for Lilly, Sandoz (pre-Novartis), and Baxter. He can speak science like a scientist at one moment and like a business-wise executive the next. He explains how Abivax emerged from a convergence of research streams into viral interference, immune-response modulation, and protein-RNA interaction targeting.

"We actually go back to the early 1990s when Jamal Tazi, a molecular geneticist and professor at the CNRS (Centre National de la Recherche Scientifique), was studying the bioprocessing of viral RNA (ribonucleic acid). Around 2006, he realized the process can be modulated pharmaceutically." Tazi knew Philippe Pouletty, M.D., then the managing director of Truffle Capital, a Paris-based venture fund. The idea immediately attracted Pouletty, a physician and immunologist, and he subsequently founded a company, Splicos, around the IP in 2008. Together with medicinal chemists at the Institut Curie in Paris, the company started to develop a library of more than 1,000 small molecules selected for their potential effects on targeted protein-RNA interactions, primarily to inhibit the biogenesis of viral RNA.

In time, the collaboration grew to include Wittycell and Zophis. Later, the three companies merged to form Abivax, giving it the three basic platforms of the merged companies, designated as antiviral, immune enhancer, and polyclonal antibodies. Abivax continued to screen the library of compounds, and one molecule, the basis of ABX464, produced a strong signal against an RNA target in HIV. The company then shifted from its primary focus on vaccine-related programs to developing the molecule into a therapeutic drug candidate.

ABX464 initially targets HIV's need to transport a large chunk of viral mRNA from the nucleus of an infected cell to the endoplasmic reticulum to induce synthesis of three structural viral proteins. A viral protein called Rev blocks cellular enzymes that would otherwise chop the large piece of mRNA to bits. The result is radically lowered viral loads through impeded reproduction and also — as it turns out — by immune enhancement. Some remains of the chopped-up mRNA inside reservoir cells that harbor the virus may be translated into antigenic peptides deposited on the cells' surfaces, exposing them to immune recognition and attack. Hence, the viral reservoir may plummet over time, impaired from triggering a reappearance of the virus after anti-viral therapy ends.

Keep an eye on Abivax. What I just described could accomplish a revolution in HIV treatment, with a realistic emphasis on the subjunctive. Phase 2 trials for ABX464 have been encouraging, as in lending courage when it is most needed in drug development — at the precipice of Phase 3.

HARTMUT EHRLICH, M.D.
CEO

Vital Statistics

24
Employees

Headquarters
Paris, France

Finances

2008 & Later
$47-53M
Truffle Capital invested in Abivax and its legacy companies.

2015 IPO
$67M
Raised – Paris Exchange

Partners

Evotec
R&D, novel antivirals

Centre National de la Recherche Scientifique (CNRS)
scientific research

Institut Curie, Paris
expand library of antiviral compounds

Latest Updates

September 2017:
First patient dosed in three-month cohort of Phase 2A study of oral ABX464 in HIV-suppressed patients.

September 2017:
Abivax and Evotec enter into strategic collaboration to develop novel antiviral agents.

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Sophie Kornowski-Bonnet, Ph.D.
Head of Partnering, Roche

Listening to Sophie Kornowski-Bonnet, Ph.D., talk about Roche's approach to partnering is overwhelming. In her distinct French accent, she recounts anecdote after anecdote of a 30-year pharma career that spans not only multiple companies but multiple continents.

It's no wonder she landed at Roche, a company rich with successful and long-running partnerships with companies such as Chugai Pharmaceutical. That commitment to partnering is even more evident when you notice that Kornowski-Bonnet, the company's head of partnering, also serves on the senior leadership team — a rarity among top biopharma companies. That's not the only fact, though, that could be considered unusual when talking about Roche's approach to partnering.

A FOCUS ON INDEPENDENCE AND AUTONOMY

According to Kornowski-Bonnet, there are three ways companies typically approach partnering. "Some companies have a completely independent partnering group tasked with finding and evaluating innovation," she explains. "They invest almost independently, and if they like it, the innovation is brought back into the company to be integrated into the pipeline." Another model involves the partnering team reporting to either R&D or commercial. The partnering team at these companies is basically trying to fulfill a request, such as finding a drug for a specific disease. Roche takes more of a hybrid approach.

"The Roche Partnering organization was established to collaborate and coordinate in full alignment with pRED [pharma research and early development], but still be independent and autonomous," she explains. "If your partnering organization is embedded within R&D, you might end up thinking or feeling in ways similar to them, which doesn't allow for the proper distance required to make big, bold decisions."

The concepts of independence and autonomy permeate any discussion regarding Roche's partnering organization. That seat Kornowski-Bonnet holds on Roche's executive committee also makes her directly report to the CEO. That's a different structure from what is in place for her Genentech Partnering counterpart. It is different still at Chugai Pharmaceutical. Back in 2001, Roche acquired a majority stake in the Japanese company, but for the most part, Chugai still operates independently. "We license and develop Chugai products for patients around the world. If we have something from outside of Japan that we think could be attractive to Chugai and the Japanese market, then my team would be ready to support." In other words, though she sits on Chugai's board, how the company approaches partnering is fairly independent of the overall Roche organization.

She admits the different structures established for Roche's various partnering organizations can be demanding. "It shows you just how challenging my mission can be. I'm looking for early-stage innovation for pRED (pharma), innovation for the Roche group (business operations), coordinating with gRED (Genentech research and early development organization) so we aren't duplicating efforts, and working with Chugai on numerous projects we established during our partnership."

THE CHALLENGES OF MANAGING A GLOBAL PARTNERING ORGANIZATION

As an organization, Roche Partnering consists of about 90 people geographically dispersed around the world and organized under the following six disciplines:

- Immunology, Infectious Diseases, and Specialty Care
- Neuroscience, Ophthalmology, and Rare Diseases
- Oncology and Cancer Immunotherapy
- Collaborations with Academia
- Innovative Technologies
- Personalized Healthcare

"The team is scientifically focused and commercially seasoned, so they are able to evaluate innovation in a deep way," says Kornowski-Bonnet.

Having this kind of a diverse and globally dispersed organization creates its own set of opportunities, as well as challenges. For example, just getting the whole team together — physically — is so difficult that Kornowski-Bonnet says it happens only once a year. That challenge, though, breeds opportunity. "We don't look to these meetings as a way of simply reviewing how we are doing as a partnering organization," she explains. "We dig into topics that are helpful to the team." For example, at this year's gathering they explored the concept of agility and how to grow and improve at it. There's also time spent on team building. "Oftentimes, we are very transactional and busy in our work, which involves a lot of travel," she explains. "So we try to slow down a bit during these off-site meetings to improve how we engage with one another as a team."

The Roche Partnering group also gets together with Genentech Partnering (the organization that does deals on behalf of gRED) every other year to align on best practices. This is a smaller group involving senior leaders of the two partnering organizations. Senior leaders of Roche Partnering also meet Chugai's partnering team on an as-needed basis.

THE ROOT OF EXTERNAL PARTNERSHIPS

The Roche group currently has 222 active external partnerships. When asked for an example of one that has been working well, Kornowski-Bonnet is quick to reference Chugai. "Initially, Chugai was an agreement to share each other's pipelines and, whenever interested, to opt in on each other's research," she notes. "But as the relationship has grown, we've been able to share tremendous knowledge while keeping our research organizations independent."

The partnership with Chugai had an unusual beginning; the former Roche CEO and Chugai's CEO had a personal relationship, and they started talking on how best to collaborate. Kornowski-Bonnet says that for her team, partnerships typically begin with the identification of a product or science. "Genentech is a good example. Initially, we were focused on the medicines they were discovering and developing, but over time we became more interested in their full pipeline." And like Chugai, despite the affiliation with Roche, Genentech keeps its research independent, too.

4 KEYS TO PARTNERING SUCCESS

Kornowski-Bonnet shares that 45 percent of Roche's current R&D pipeline has been externally sourced. Further, 36.5 percent of total pharma sales are currently generated from partnered products. Such a large partnering impact means they must begin with a large amount of potentials. "We typically screen about 2,500 projects every year," she says. Some of these opportunities are brought to Roche unsolicited, while others are actively sought out by the partnering team. For example, the Roche Partnering team reviews abstracts of conference programs of therapeutic interest looking for opportunities. "Being organized by therapeutic area helps us to always be in scouting mode, and we only progress on something if it makes sense," she attests.

So how often do those potential partnerships "make sense"? Of the 2,500 projects screened throughout the year, she estimates that only about 100 end up having a confidentiality agreement (CDA). In 2016, Roche Partnering closed 44 partnering deals. (For a sampling of those made public, see table at right). Some of the deals Kornowski-Bonnet references by name include GNS Healthcare, a company focused on precision medicine. Roche hopes to leverage GNS' reverse engineering and forward simulation (REFS) platform to power the development of novel cancer therapies. Some other high-potential deals she mentions include Foundation Medicine, a company using genetics to help select drugs for cancer patients; InterMune, a biotech focused on pulmonology and fibrotic disease therapies and acquired by Roche in 2014; Flatiron Health, a healthcare technology and services company; and SQZ Biotech, a privately held company developing cellular therapies.

According to Kornowski-Bonnet, almost all successful partnerships begin with scientific alignment. "We should be passionate about the same things, or we are bound to disagree at some point." To gain alignment there are key questions to consider, and those vary depending on the therapeutic area. She gives the following example:

- Can a next-generation antibody platform enable a broader target space?
- How excited are we about it?
- Which indications can be unlocked by those new targets?

Kornowski-Bonnet believes there are four keys to partnering success. First, there has to be a common interest in the science. Second, there has to be an honest relationship based on transparent information and knowledge sharing. Third, there needs to be an appetite for collaboration and a willingness to work together and learn from each other. "This is really important because if someone knows it all, has done it all, and can do it all, they are not going to be

RECENT ROCHE PARTNERING DEALS MADE PUBLIC

COMPANY	DEAL
Halozyme 09/20/2017	License agreement with Halozyme Therapeutics for the development and commercialization of subcutaneously administered therapeutics
Dermira 08/08/2017	License agreement with Dermira on its IL-13 monoclonal antibody lebrikizumab
Vital Art and Science 06/19/2017	Agreement on use of VAS mVT app service across Roche's ophthalmology portfolio and real-world data access
GNS Healthcare 06/19/2017	Agreement on use of machine learning platform to investigate factors that impact efficacy and safety of cancer therapies
BMS 04/13/2017	Development of anti-myostatin antibody with best-in-class potential for Duchenne Muscular Dystrophy
ImmuNext 12/20/2016	Exclusive license and collaboration agreement to develop and commercialize therapeutics that agonize the VISTA signaling pathway
Monash University 11/14/2016	Early-stage research collaboration focusing on proteins for the treatment of autoimmune diseases
Halozyme 11/10/2016	Clinical trial collaboration to combine Tecentriq and Halozyme's PEGPH20 in up to eight different cancer types

a productive partner — for anybody." Finally, members of the partnership need to have a problem-solving mindset. "When you have a problem — and you will have problems — you need to decide if it's important, why the problem happened, and how to collaborate on finding solutions that are the best for both." She says usually you can tell from the first meeting which of those keys to success are present and which are going to be lacking.

WHEN PARTNERSHIPS DON'T GO AS PLANNED

Kornowski-Bonnet explains the partnering process is similar to a scientist in a lab who wants to gather enough information to determine if a potential drug should be "killed" early so as to not waste time and resources. Usually when a partnership doesn't work out, she says, it's due to the science. "That's OK, though; it's all part of R&D."

But every now and then, she admits the company has to discontinue a relationship because it isn't worth trying any harder. "We could go back and redesign a study, but sometimes you just need to know when to say enough." Not being able to trust a partner is another reason for failed collaborations. If it's too challenging to interact due to misaligned expectations or a lack of transparent information sharing, then a partnership is usually ended quickly.

"When I hit a roadblock in a partnership, I take the time to reflect and use it as a learning opportunity to improve how I approach the next partnership. I value the projects we terminate just as much as the ones we pursue. This helps you to not only know the difference between the two, but improve upon the deals you will do later."

It's a risk pursuing any partnering deal, especially in terms of time and manpower. For those deals that look *really* interesting, between 20 and 100 people may be involved to just complete the due diligence step. At Roche, some of the people involved in that process are the members of pRED who help determine if the innovation is something to integrate into Roche's portfolio. But Kornowski-Bonnet stresses that there is more to it than ticking off boxes when it comes to Roche's approach to partnering. "A deal is a story between people. I reinforce with my team that they need to pay attention to the 'electricity' that takes place between people and the flow of engagement between parties, as all of that is nearly as important as the quality of the data and the science. Because when you sign an agreement, you will be wedded for a long time with *people* — who are now your partners." L

From Startup To Acquisition By Lilly, And Everything In Between

ROB WRIGHT Chief Editor @RfwrightLSL

Daniel Skovronsky, M.D., Ph.D., Lilly

In the first six months of Avid Radiopharmaceuticals' existence, it was hard to find the company on a map. That's because, according to the wife of Daniel Skovronsky, M.D., Ph.D., Avid was literally being run out of Daniel's car. "I did not have an office, and my wife would tease me that I *really* didn't have a company. 'It's just a PowerPoint presentation on your computer,' she'd say," he recalls with a laugh.

She wasn't wrong, considering most days her husband was spending almost all his time driving to appointments, showing his presentation, and asking for funding for an idea he had first hatched as a graduate student at University of Pennsylvania School of Medicine. It was the stereotypical entrepreneur's life, rife with those elusive and rare euphoric wins that inevitably are followed by a glut of letdowns and disappointments.

Skovronsky's story does (spoiler alert!) have a happy ending, though — that is if you consider $300 million a lot of money to be paid for a pharma company that, when started, didn't even have the license for the technology idea it was touting.

A New Approach To Identifying Alzheimer's

While at Penn, Skovronsky was doing autopsies and studying the brains of people who had died with Alzheimer's disease. He soon wondered if they could use medical imaging technology to detect for Alzheimer's while a patient was still alive. He and the team of academic investigators at Penn started with the same dyes they had been using to stain the tissue on a glass slide for microscope analysis. "We began doing chemistry to try to turn those dyes into a drug that we could then make radioactive and see in a brain," he explains. The goal was to develop a molecular imaging agent that could detect the presence of Beta-amyloid plaque — a defining pathology of Alzheimer's — in the brain. After a few years of research, the team applied for NIH grants to fund the work they were doing. "For whatever reason, the grants got denied. So, I said, 'We should start a company around this. Then we'd have tons of money,'" says Skovronsky. Of course, he quickly found out it wasn't going to be that simple.

What To Consider When A Bid Is Made For Your Company

When Daniel Skovronsky, M.D., Ph.D., got a call from Lilly about the Big Pharma acquiring his company, Avid Radiopharmaceuticals, he knew it was a serious bid. He and his board of directors had previously discussed what amount they would consider in case such a call ever came, and Lilly was in that range.

There were other bidders, and although Lilly was ultimately chosen, it wasn't simply because they had the highest bid (they did not). According to Skovronsky, one of the biggest factors he and the Avid board considered was Lilly's reputation of nurturing, sustaining, and continuing to build companies after they were acquired. Some of the other companies admitted their plan would be to buy the company, disaggregate the team, and focus on the asset. Skovronsky thought hard about the various prospects and discussed them with his board. "I told the board that, essentially, we had three constituents. First are the investors, who will weigh the short-term up-front money of the deal versus the milestones and royalties down the road. The second group is the employees. As their boss and the person who convinced them to join the company, I wanted to make sure they had a good opportunity after the company was bought. Finally, there are the patients. We had to make sure the product and the technologies being developed were in the best hands capable of being successful. After all, our mission was not to just diagnose Alzheimer's, but to make it possible to develop treatments for Alzheimer's disease. That's how we decided Lilly would be the best choice for the future of the company."

A Catch-22

In 2004, before jumping into the deep end of the entrepreneurial pool, Skovronsky did his homework and talked to a lot of people in the industry. "Many pointed out how risky it was to start a company and how the majority of startups typically fail," he says. "I actually agreed and realized that many things could go wrong." And go wrong they did, starting with his initial plan of raising money, hiring staff, and licensing the technology.

Although Skovronsky was one of the inventors of the early-detection technology for Alzheimer's, at the time, its license still belonged to his employer — the University of Pennsylvania. He soon discovered that most investors weren't interested in committing if he didn't own the license. Similarly, Penn said once he got the money, they'd write a letter saying they'd license the technology to him. "It was like a Catch-22. In hindsight, I was pretty naive about what it took to actually start and run a company, and I was oblivious to how infinitesimally small my odds of success were."

$1 Million Is A lot Of Money — Until It's Not

After pitching a few VCs, Skovronsky learned they wanted to hear his exit plan, which he quickly summarized into three options— IPO, sell the company, or go it alone. Eventually, his pitch worked, and he received his first round of funding. "It was 1 million dollars," he reflects. "At that time I was working with my local neighborhood bank because it was close to my house." When he called the bank to see if the money had shown up in the account, he recalls the teller being flustered. "Yes, it's here, $10,000. Wait. No, no. What? Oh my gosh, it's *1 million dollars*!" she gasped. "I've never seen this much money in an account." It was then Skovronsky realized he was probably going to need to switch banks, which he eventually did.

"I remember thinking that with 1 million dollars we were guaranteed to be successful," says Skovronsky. "After all, a million dollars is *so* much money." Still, he soon learned he would have to raise a whole lot more.

For the next five years Skovronsky continued to raise additional money and, with his team at Avid, successfully took the amyloid imaging agent through clinical trials and towards FDA submission. It was during this time that Lilly had shown interest in acquiring Avid. But even a few months prior to his company being acquired, Skovronsky was still out pounding the pavement for funding, filing the company's Form S1 (used by companies planning on going public to register their securities with the U.S. SEC), dealing with bankers, and doing a non-deal road show (i.e., when an executive holds discussions with potential investors but nothing is offered for sale). The company also was filing its new drug application with the FDA — a massive undertaking, especially for a startup. Once Lilly started the due diligence process, Skovronsky was deeply involved in managing that, too. "Going to medical school, completing my residency, and pursuing my Ph.D. were a cake walk in comparison to being the CEO of a biotech," he says with a laugh. "It was not uncommon that I would work from 7 a.m. until 11 p.m., come home, go

to sleep, and do it all again the next day, with lots of travel mixed in."

Just before the sale to Lilly in 2010, Skovronsky says he had raised around $60 million. "I thought *that* was a lot of money. But when we sold the company for $300 million [with potentially $500 million more in contingent milestone payments], I thought *that* was a lot of money." Today, the former CEO is now an SVP for science and technology and president of Lilly Research Labs at Lilly. "At Lilly, we invest about $5 billion a year in R&D. Now *that's* a lot of money."

Why Not Just Retire?

The sale complete, the entrepreneur had one thing left on his bucket list, which didn't include joining Lilly long term. "After being so busy for so long, I just wanted to make sure the drug we had been developing got through the FDA," he confides. Turns out, this was not going to be easy. About a week after the deal closed, the FDA informed Lilly they were taking Florbetapir (the name of the company's PET scanning radiopharmaceutical compound) before an advisory committee. A few months later the agency said they were not going to approve it.

> In hindsight, I was pretty naive about what it took to actually start and run a company.
>
> DANIEL SKOVRONSKY, M.D., PH.D.

Understandably, Skovronsky was nervous. He didn't want Lilly to think he had duped them, so instead of retiring to Hawaii or some other tropical location, he decided to stick around to make sure Florbetapir got approved.

It was during this time that he really got to know a number of Lilly's leaders. He spent a lot of time with John Lechleiter, Lilly's CEO at the time; Jan Lundberg, head of R&D; and David Ricks, then head of U.S. business (the current CEO). According to Skovronsky, all three were interested in understanding the facts and circumstances behind the FDA's denial, which helped provide a clear path forward. In early 2011 the FDA gave its approval.

Many people thought Skovronsky would leave Lilly after the FDA approval. But, during his early days at Lilly, he says he enjoyed learning about the other parts of the business, and he eventually took on more responsibilities. He explains that, as part of the deal he made with Lilly, "There were no golden handcuffs or strings of any kind. I got all my money in cash the day the deal closed, and it wasn't contingent on me continuing to run Avid."

Another question he gets frequently asked is, "Why are you still here?" "This was actually one of the most frustrating things asked of me during my first couple of years at Lilly," he concludes. "I understood their perspective, and it took me a while to earn their trust and confidence — and to prove that I actually cared about Lilly as much as they did." L

How Daniel Skovronsky Went About Valuing His Company For Sale

Even before Avid Radiopharmaceuticals was being courted by multiple – and larger – acquisition suitors, Daniel Skovronsky, M.D., Ph.D., the company's CEO and founder, had been trying to determine the value of the company. While Skovronsky admits he doesn't have an MBA, he says he has learned a lot about venture capital, valuation methods, and cash flows from his entrepreneurial experience. Thus, he wasn't inclined to simply leave this decision up to his banking partners.

"I *never* just say, 'I am going to leave that up to the experts.' If I don't understand something, I tell the person to teach me, as I will take the time to figure it out. Despite what the experts tell us, determining valuations, cash flows, etc. is not as hard as drug development," he says.

Skovronsky says one way to determine a company's valuation is sort of a past view, which he admits is the most primitive. "Basically, you put this much money to work, for this long, and your biotechnology investors need 'X' kind of return. It has little to do with the value created." Another approach is to look at a company's current stage of development, with what product, and with what kind of potential. "You try to look at companies that were in similar situations as yours, and compare similar transactions." A third way takes more of a future view. "Where do you think you will be five years from now, and what kind of revenue will you have? You assign a multiple to determine what you think it will be worth." He says Avid used pieces of all three methods to come up with its valuation.

INDUSTRY EXPLORERS
BLAZE ON

The stories of longtime leaders, still active in the industry, sharing their historical perspectives on life sciences industry innovation.

WAYNE KOBERSTEIN Executive Editor @WayneKoberstein

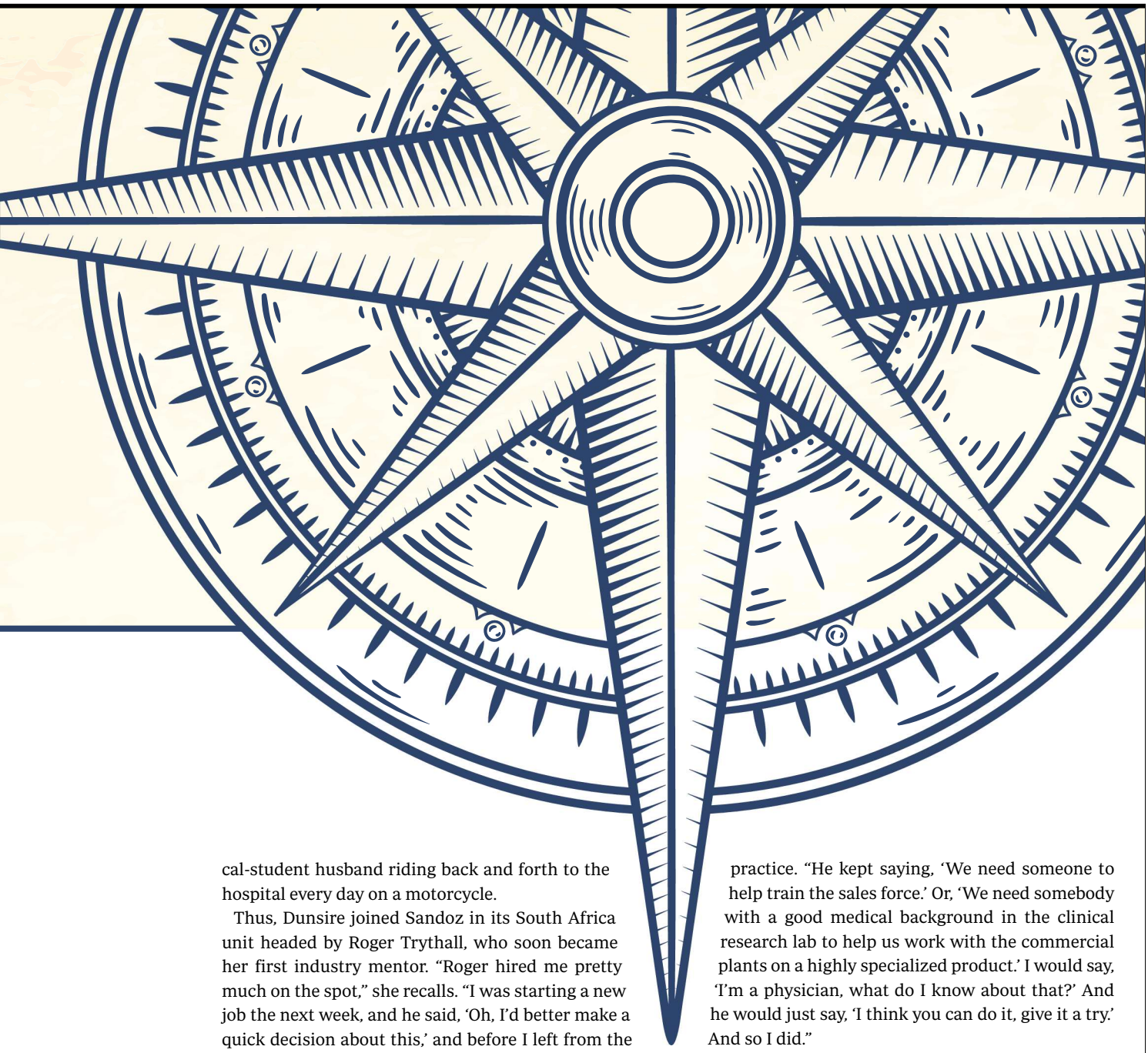
Transformation—
Deborah Dunsire

To transform: to start with a scientific hypothesis, use it to create or isolate a potentially therapeutic substance, devise and conduct bench tests, move the compound into preclinical, then clinical trials, and with a great measure of luck, finally gain approval to take the drug to market and make it available to patients. Some people disdain the drug-commercialization process as fraught with fraud and conflict of interest. Others celebrate it as ... pure magic. In the latter camp would be Deborah Dunsire, who has lived and worked in a world driven by commercial drug development for three decades.

Dunsire is now president and CEO of tiny XTuit, though her roots are solidly in Big Pharma as a 17-year veteran of Sandoz/Novartis and subsequently head of Millennium pre- and post-Takeda. In her extraordinary career, she has traveled from her original home base in South Africa to Europe and the United States with the eager support of her companies and the people around her. She is aware of the barriers that can confront women executives in the industry, but she has personally sailed right past the most daunting ones, perhaps as an exception that proves the rule. She shows none of the arrogance that you'd think would be required to suggest her experience is something all industry women can have through hard work alone, and her life is full of useful lessons for matching accomplishment to good fortune.

Drawn By Development

Transformation of science to medicine, and the prospect of joining in, served as the compelling force that drew Dunsire into the industry. With a medical degree from the University of the Witwatersrand, she served for a while as a busy family practitioner, then in an emergency room filling time before the planned start of a residency in ophthalmology. Between the two jobs, in 1988, she read a newspaper ad by a pharma company for a job in clinical trials. She had just married and returned from her honeymoon with nine months still to wait for the residency. She thought the clinical research job would be useful for her planned career, and the position came with a company car, which may have tipped the scales. The car alleviated her worry, heightened in her ER experience, about her medi-



cal-student husband riding back and forth to the hospital every day on a motorcycle.

Thus, Dunsire joined Sandoz in its South Africa unit headed by Roger Trythall, who soon became her first industry mentor. "Roger hired me pretty much on the spot," she recalls. "I was starting a new job the next week, and he said, 'Oh, I'd better make a quick decision about this,' and before I left from the interview that day, they told me I had the job."

Dunsire began at Sandoz intending to stay only the nine months until her residency commenced, but the actual experience changed her mind completely.

"I became totally captivated by the impact of scientific knowledge transformed into medicine and how that, in turn, could transform lives," she says. Her work immersed her in clinical trials for new drugs related to the big Sandoz product, Sandimmune (cyclosporine), for preventing organ rejection in kidney transplantation. There, she says, she observed how the lives of transplant patients changed when stabilized on adequate immunosuppression — something impossible before Sandimmune.

Meanwhile, the CEO offered Dunsire a variety of career paths to contemplate, not in theory but in practice. "He kept saying, 'We need someone to help train the sales force.' Or, 'We need somebody with a good medical background in the clinical research lab to help us work with the commercial plants on a highly specialized product.' I would say, 'I'm a physician, what do I know about that?' And he would just say, 'I think you can do it, give it a try.' And so I did."

While working on the development of Sandostatin (octreotide) for treating the harsh symptoms of some rare tumors, Dunsire relied on advice from many experts in Sandoz around the world to stretch her small budget. A trip to a related conference in the United States offered a unique, long-term opportunity. There she met two other people who became influential in her career: Daniel Vasella, future chairman of Sandoz and Novartis; and David Epstein, who would later head the Novartis Pharmaceuticals Division. Vasella was then the product director, and Epstein, the product manager, for Sandostatin and other drugs.

"It was great to have access to the tools and approaches used in the United States to help expand in South Africa," says Dunsire. "Daniel and David were very generous with their time and their ideas, and they con-

tinued to be mentors in my career. Actually, I worked directly for David Epstein for 11 years when he was head of Novartis Oncology, which was an incredible period of time in Novartis history."

The meeting portended big changes in Dunsire's future. Back in South Africa, the more she took on new assignments and higher responsibilities, the more she enjoyed the experience of global drug development. Early on, she had decided to stay with Sandoz rather than return to her planned residency. Several years passed, and once more Trythall pointed the way for her further development. He told her HQ experience would be critical and so, to grow, she moved to Basel, Switzerland, site of the Sandoz headquarters. With his support, she landed an assignment as an international product director, heading the global launch of Sandimmune for autoimmune disease, and she moved to Basel in 1991. Besides taking her into a new therapeutic area, from transplantation to autoimmunity, the job at Sandoz headquarters transported her to a higher level of involvement with the wider world her company and industry covered.

"I recommend to anybody building a career in our industry, if there is an opportunity to work in a different country, take it," she says. "From a personal growth perspective, it's an incredible stretch. You have to think about why you do something a certain way and why people in other places do the same thing differently. It challenges your assumptions in so many ways. Global jobs are particularly like that. Not only was I now living in a different country, but I was working across many countries."

One early lesson: After organizing an international meeting of company experts in Madrid, she found the Spanish custom of late-night meals doomed her plans for a 7 p.m. dinner. "You learn so many things about the cultures, about the people, and about how they live, so it was a very rich time for me in Basel."

For drug-development strategy, the international differences can be much more challenging and consequential. "At that time, Europe was many countries rather than a single, united region, and we had to deal with how each health authority affected approval and marketing," she says. "Just bringing together groups of passionate product leaders from all of those countries and navigating through a common strategy together was a true growth experience."

From Europe, Dunsire's responsibilities also took her to Japan, where cultural differences can present even steeper challenges in drug development. "For example,

One Woman's Industry Journey

Even though Deborah Dunsire has done extremely well as (not for) a woman in the traditional man's world of Big Pharma, she still sees institutional and cultural barriers to the advancement of women in the industry. In the following, she describes her experience and observations of the issue in her 30-year career.

I honestly can't identify an obstacle I've faced that was driven by me being a woman, although I've certainly faced obstacles. But can I see it in the industry and do I see women who have been affected? Yes, I do. One of the things that I've faced, perhaps without realizing it, is the difference in how women are perceived in a conflict situation compared to men. If there's conflict, a man is seen as strong, but a woman may be seen as strident. Have I seen improvement? Oh, yes, I certainly have. There are more women in CEO roles and more first-time female CEOs now than there were 10 years ago. When I came to Cambridge, there were maybe two other female CEOs in the biotech space. The landscape has shifted. Of course, there's been an incredible, unprecedented rate of companies starting up in the last 10 years, particularly in the last five years, but we also have more people who are open to seeing qualified women as able to lead and raise money for an organization. There is the odd pocket of male-chauvinist behavior – but thankfully few and far between.

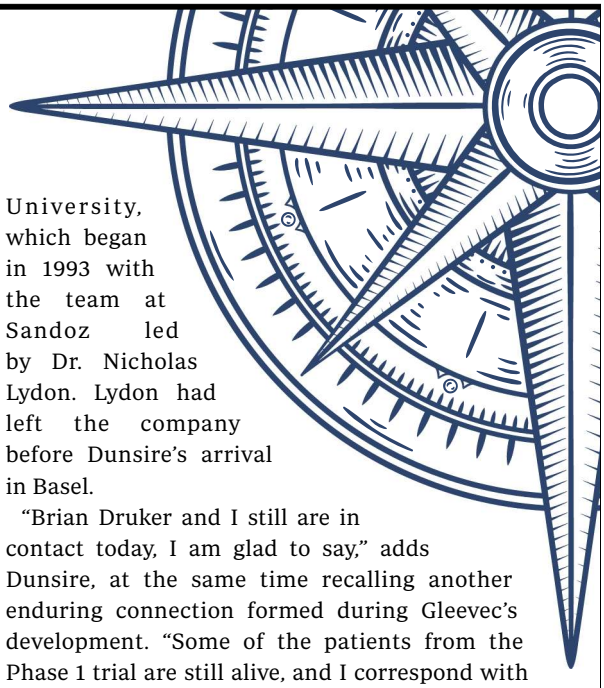
there were instances where the regulatory authority would want us to use half the dose that we used in the rest of the world, and we had to manage the best development for patients across countries without creating conflict across the global environment because of it."

> **"I recommend to anybody building a career in our industry, if there is an opportunity to work in a different country, take it."**
>
> **DEBORAH DUNSIRE**
> President & CEO, XTuit

Building Oncology

Dunsire spent several happy years in Basel. But a much larger opportunity, and an even bigger change in location, would soon transform her life again — a move to the United States, along with a move up in professional responsibilities. After taking a VP position at Sandoz U.S. headquarters in New Jersey, she answered a call from Epstein, then leading the Specialty Businesses Division, to begin building an oncology strategy and organization that would eventually have a global reach for Sandoz. "The Sandoz oncology business was initially very small, and then in 1996 all of a sudden we became Novartis!"

Not that the merger of Sandoz and its across-the-Rhine neighbor Ciba-Geigy added much to the oncology franchise. As Dunsire explains, Ciba-Geigy had previously licensed the rights for its biggest cancer drug, Aredia (pamidronate), to Chiron for a period, leaving little of significance in the area. She describes the early days humbly, but with humor: "I always say I was given the opportunity to lead the oncology unit because it was so small and probably didn't matter much to Novartis!" Fortunately for her fledgling unit, Novartis executed a contract clause that allowed it to bring Aredia back into its product line, which kick-started its oncology business while it developed new compounds in the pipeline. Notably, two of those compounds were Femara (letrozole) and the now legendary Gleevec (imatinib). Throughout Gleevec's development, Dunsire, Epstein, and the development team worked closely with Alex Matter, the chief scientist for oncology, and Elisabeth Buchdunger, a member of the Sandoz team that helped discover imatinib. The Gleevec project was accelerated by a collaboration with Dr. Brian Druker at Oregon Health & Science University, which began in 1993 with the team at Sandoz led by Dr. Nicholas Lydon. Lydon had left the company before Dunsire's arrival in Basel.



"Brian Druker and I still are in contact today, I am glad to say," adds Dunsire, at the same time recalling another enduring connection formed during Gleevec's development. "Some of the patients from the Phase 1 trial are still alive, and I correspond with one of them, Virginia Garner. Virginia was close to dying, having had CML (chronic myelogenous leukemia) for three years when she went on the Phase 1 trial in 1998. Today, she is still running marathons — half-marathons now — to raise money for the Leukemia & Lymphoma Society. I sponsor the marathons and get her newsletters, and we exchange cards at the holidays. Those cards are some of the most rewarding things in my life, because they remind me I was part of something that made such an incredible difference to so many people whose disease previously would have killed them."

Until Gleevec, only a few companies had attained any success with new drugs for cancer. For the work-in-progress oncology group at Sandoz/Novartis to score such a victory was frankly astonishing. But Dunsire believes the innovative cultures at Sandoz and Ciba-Geigy, combined in Novartis, explain how the extraordinary feat occurred.

"Sandoz was always a very science-driven company working on medicines that made a difference. It had an eclectic mix of compounds, but they were very innovative. From cylosporin for organ transplantation, all the way down the line to Gleevec, it's been a very innovative company. Ciba-Geigy had a similar great heritage of innovation. When I hear people criticize Big Pharma about the ability to innovate, I always tell them a lot of the innovative products in the Novartis line came from within. Gleevec, the first targeted agent approved in oncology, went through complete development, from first-in-human to approval by the FDA in only four years and four months, which is unprecedented, because it really works. But it also was because of the company's commitment to the science and to collaborating with academia and clinical researchers to really fully understand what the drug could do."

Dunsire helps clarify some of the mythology that has grown up around Gleevec; namely, the widely reported

email campaign by patients in the trials that supposedly convinced Vasella to overrule his own scientists and order the product's development to continue. The emails came *after* the decision to proceed, she says.

"David Epstein and I went to the New York offices to talk to Daniel about continuing the development after analyzing the market and finding it would be small. How wrong were we? But we said the data is so good, we can't walk away. So we agreed in that meeting, even though the forecast for the market was tiny, that there was nothing else for us to do but keep going. The email campaign actually came further down the line. We didn't have a commercially scaled process by the time we knew the drug was spectacularly effective, so we didn't have enough supply for all the patients who needed to be on the drug. We had to delay the Phase 2 trial to make sure the Phase 1 patients could continue to get the drug, and that caused a lot of email traffic from patients, which was empathetically received, but it wasn't the difference between the drug proceeding or not; that decision already had been made."

For all of its value, Gleevec may have obscured a broader accomplishment on Dunsire's watch — building the oncology organization practically, as one biography states, "from the ground up."

How do you build organizations from the ground up — especially after a major merger? Start by keeping or bringing in people with the right skills and motivation, she says, then adds a realistic caveat:

> **"When I hear people criticize Big Pharma about the ability to innovate, I always tell them a lot of the innovative products in the Novartis line came from within."**
>
> **DEBORAH DUNSIRE**
> President & CEO, XTuit

"If you can bring on a team of people who are passionate about transforming outcomes for patients, it is easier to unite around that goal and create the new culture. With that focus, the conventional wisdom on big-company mergers — as in 30 percent of the staff will turn over before the different company cultures really start to meld — can be mitigated."

With the oncology group, Dunsire's challenge was even greater because she inherited no definite plan. That was the "from the ground up" part. Instead, she says, "It was a constant surprise for me. Novartis Oncology is now over a $10 billion business, but when it started out, there was no specific corporate strategic plan to build an oncology business or to invest in oncology as a company pillar. It was driven by doing the right thing for the patients and having innovative products in the pipeline. We came together to deliver transformative medicines, and gradually the organization emerged. I was privileged to be its leader."

Millennial Leap

Dunsire remained at Novartis oncology for many years and led the development of numerous other drugs in the cancer area. Not all of them treated cancer itself; a few addressed ancillary conditions such as tumor-caused fractures. As she describes, it was not a top-down, command-and-control portfolio, but a variety that genuinely reflected the relatively opportunistic style of the company and the oncology organization built under Dunsire's leadership.

Nothing, as they say, lasts forever, and the best things in life never last long enough. When Dunsire answered an outside opportunity after 17 years at her first and only company, one could argue it was a good time to move on — because she was sorely needed in a much younger sector of the industry. In 2005, when she took the CEO position at Millennium, that company wasn't performing as expected. Most people around the industry at the time will remember that Millennium's single major product, Velcade (bortezomib), had fallen far short of projections and its sales had plateaued in its only approved indication, relapsed/refractory myeloma. But the company had great people and a promising pipeline, and Velcade still had a much larger potential.

Not that the decision to leave Novartis came easily. Dunsire knew she wanted to extend the reach of her responsibility from the commercial area to include the span of R&D. She was already covering much of that ground in her position at Novartis and envisioned herself as the chief executive of an entity that contained the entire span of functions from science to market. In the traditional career path at Novartis, her next step would likely have been running a regional division, such as South America. Yet, even though that role would have increased her commercial role tremendously, it would also have encompassed the company's entire product line, not just the innovative side. "I've always wanted to work on the leading edge of therapeutics for diseases that are truly unmet by the available medicines," she says.

As she was contemplating her next move, she received a call from a recruiter who offered her a job that fit all of her criteria. "Millennium had all of those

"I honestly can't identify an obstacle I've faced that was driven by me being a woman, although I've certainly faced obstacles."

DEBORAH DUNSIRE
President & CEO, XTuit

elements. It was focused in oncology and inflammatory diseases, and it had a reputation for phenomenal science, drug discovery programs, a pipeline in development, and a transformative oncology product already on the market."

But that major oncology product needed help, and the company needed more commercial clout. Founding CEO Mark Levin, who was the first person Dunsire met at Millennium, moved quickly to introduce her to his team and place her in his job. "Mark was an iconic leader, and the people within the company loved him. He made the transition easy for me because he told them, 'We need a new leader for this time in the company's life. We know we've got to be more successful commercially, and I believe this is the person who can help us do that without losing focus on driving our science forward.' Watching Mark, I learned so much about vision, how people are inspired, and how extraordinary things are accomplished when people have a vision. I'm eternally grateful to him."

After the meeting with Levin and the company staff, Dunsire met with the members of the board. First was Dr. Eric Lander at the Whitehead Institute in Cambridge, MA, a persistent driver of academic-to-business startups and outspoken advocate of new technologies such as CRISPR. "Eric offered me tea — real English tea. Of course, he had been a Rhodes Scholar at Oxford, where he studied mathematics. The entire Millennium board was made up of stellar individuals. I was so privileged to work with them in my first CEO role."

In her first days at the company, she focused on the commercial organization. "Millennium was a company deeply rooted in the science. They had the idea that science is hard, and once the science is good, everything else is easy. But they had come to realize that wasn't necessarily the case. I guess my job was to tell them it's *all* hard. Science is indeed hard but commercialization requires the same hard effort and the same degree of outstanding talent. At the same time, even with my commercial background, they could trust me not to obliterate the products of the future, but to nurture the development pipeline."

When Dunsire came on board, Millennium was divesting all of its core cardiovascular assets, including Integrilin (eptifibatide), to its partner Schering Plough. She says cocommercializing the products would have made them even more of a distraction than in-house management, blurring the company's focus on oncology and ability to recruit the right team in that area. "I sound like a broken record, but with Velcade, we ultimately attracted a number of people extremely enthusiastic about leading the commercial team. I was able to hire Dr. Christophe Bianchi from Sanofi, and he's an extraordinary commercial leader. With Velcade, the solution was getting the right team, simplifying the way it was promoted, expanding the sales force — doing things that I had done for years." And as others have noted, subsequent approvals moved Velcade from third-line to first-line use. "Velcade is one of those life-transforming products for myeloma patients. It grew up into an incredibly successful brand, now close to $4 billion worldwide."

Dunsire also fulfilled her commitment to moving new drugs through the pipeline and into the market. One was vedolizumab (Entyvio), the antibody of integrin α4β7 (LPAM-1, lymphocyte Peyer's patch adhesion molecule 1), for ulcerative colitis. "Vedolizumab is an extraordinary drug, and it might never have happened

because it was partnered with Genentech and neither one could figure out how to make a stable cell line. Eventually, Genentech gave the product back, along with some very good clinical data the two companies had on the drug. I looked at that data and said, 'This drug works. We've got to find a way to do this.' But I said to the team, 'We can't spend money on it forever. You've got six months. If you can figure out the cell line, then we'll go forward.' The protein science team at Millennium did figure it out, and after many ups and downs, the product came to market."

An oral proteasome inhibitor to treat relapsed or refractory multiple myeloma was the next challenge. Dunsire and the R&D team debated at length about what form the product should take and the researchers explored the alternatives. "Eventually, we found the right answer and our R&D brought forward Ninlaro [ixazomib], the world's first oral proteasome inhibitor."

Financing all of the product development led Dunsire and the company to realize it had to be more selective in R&D, which required defining the right focus in the R&D portfolio. Beyond that, she says the overarching challenge was rebuilding the confidence of the company. "When I took over there was a 22 percent employee turnover rate, and by the time of the Takeda acquisition, it had come down to well below the industry average and for years following the acquisition by Takeda in 2008, we had about 3 percent turnover."

Takeda Takeover

A mention of the Takeda acquisition, ephemerally creating "Millennium: The Takeda Oncology Company," marks the next big stage in Dunsire's career. All of my interviews with the principals seem to support this interpretation of the merger: The acquired had more influence on the acquirer than the other way around. It was primarily culture, not only commerce, that drove the deal. To no surprise, then, the acquisition of Millennium by Japan's oldest pharma company began with a personal connection that led to a meeting of minds.

Dunsire and Anna Protopapas, then head of business development, traveled to Japan to visit companies, looking for opportunities for potential in-licensing of products, partnering, research funding, and so on. One of the companies was Takeda, where they met then-president and subsequently CEO and chairman, Yasu (Yasuchika) Hasegawa.

"Yasu was truly a visionary leader of the company," she says. "If there's an inner transformation at Takeda, it was because he personally drove it." Hasegawa had lived in the United States for 10 years and Germany for three years, and had a global vision for Takeda. At first, Dunsire and Protopapas believed Takeda's only interest

DEBORAH DUNSIRE – CAREER SEQUENCE

1988 Executive Director, Clinical Research
Sandoz AG, Johannesburg, South Africa

1991 International Product Director,
Corporate Marketing Group,
Sandoz AG, Basel, Switzerland

1994 Vice President, Sandoz, New Jersey

1996 Senior VP, North America Oncology, Novartis

2005 President & CEO, Millennium, Cambridge, MA

2006 Board Member, Allergan

2008 President & CEO, Millennium (Takeda),
Cambridge, MA

2010 Corporate Officer & Board Member, Takeda

2013 President & CEO, Forum

2017 President & CEO, XTuit

2017 Independent Director, Ultragenyx Pharmaceutical

was in Millennium's science. They arranged a number of discussions between the two companies' scientific teams but never found the right formula for a partnership that worked ideally for both of them.

"Then Yasu Hasegawa asked if he could meet us during JP Morgan at a nearby restaurant. He said, 'Look, we've really thought about this, and for us to become a leader in oncology, we need a major catalyst, and we believe that bringing Millennium into Takeda could be that catalyst. We would want Millennium to be there for our oncology line.'"

Dunsire told him the timing might be difficult because Millennium was preparing for a big launch of the first-line indication for Velcade. "I said, 'We have to be successful, I can't distract people. I understand that Japanese companies can be very diligent, which can take a long time. I'm not prepared to put the company through a long process. How quickly can you do this?' And he said to me, 'Six weeks.' And lo and behold, it was six weeks."

Hasegawa proclaimed he was not buying Velcade; he was bringing Millennium in to be a transformation agent for Takeda. Dunsire said he told her, "'We need to become more global in our thinking. We need to transform, and not only can Millennium build our oncology, but also catalyze our transformation.' We were afforded the opportunity to lead oncology and to be that transforming agent within Takeda. I credit that vision to Yasu Hasegawa." (See our June 2016 feature article, "Takeda's New Plans For Worldwide Growth.")

In the five years following the acquisition, Dunsire remained at the helm of Millennium, now Takeda Oncology, leading it through an impressive period of growth. It maintained a healthy pipeline that produced a run of good products and augmented it with business development. She mentions one deal in particular, a partnership with Seattle Genetics on brentuximab vedotin (Adcetris), a successful chemotherapy for treating Hodgkins and anaplastic large cell lymphomas, with Takeda as the commercial partner. The deal connected her to Seattle Genetics' CEO, Clay Siegall, who later supported her entry to the board of Ultragenyx, a developer of therapeutics for ultra-rare diseases. Dunsire also was elevated to a board position in Takeda — a stunning first for a woman in the company.

Ultragenyx may have awakened her startup spirit, or perhaps it was all of those long flights to and from Japan, but no question Dunsire was eventually drawn away from the corporate world of Takeda as she had been from Novartis years earlier. She left the company in good reputation and took the CEO position at little Forum Pharmaceuticals, which was fighting an ultimately losing battle to develop a drug for schizophrenia and dementia.

Forum was a private, precommercial company going into Phase 3 clinical trials when she joined it in 2013. Forum's investors were all at a single firm, Fidelity, and they wanted to build a new model for biopharma companies by showing they could insulate Forum from the need for further investment or partnering as it commercialized the pipeline. "It was a mouth-watering challenge to take on Alzheimer's and then build the company around it, with the opportunity to bring the drugs through development and into the commercial realm in a new way," says Dunsire. "I had to really make the company transform from a scrappy early-stage organization and rapidly expand the operation for running four global Phase 3 clinical trials. Yet I had to be careful not to lose the essence of the company. You have to be very diligent to ensure that you build the culture you want and you retain the essence of what makes the company great and what drives people to come to the company and stay there."

After a Phase 3 trial produced poor results, however, the company folded. Dunsire has opined elsewhere on why that happened, including a possible flaw in how patients were assessed for progress. Yet, as a couple of years of failed Alzheimer's trials in multiple companies attest, no one has identified an unerring or even roughly indicative set of biomarkers for the disease.

Following Forum, Dunsire got right back on the horse in her current job as CEO of XTuit which has taken on therapy-blocking fibrosis in cancer. "XTuit is the earliest company I've run, and it's like being in a small boat, very close to the ocean so you can feel the waves," she says. "If you're on an ocean liner, you look down and the waves are somewhat distant. Here I have the fun of creating the team, leaning into the science, and taking it forward. There is a lot of excitement, and a lot of roller coaster feelings as well."

She came to XTuit with a lead from a longtime colleague at Millennium, Dr. Alan Crane, the founding investor of the company's drug platform for clearing the tumor microenvironment of fibrotic tissues that could keep other therapeutic agents from reaching the cancer. "This company is focused on normalizing the aggressive microenvironment to reverse fibrosis and make cancers treatable, and that's a big mission," Dunsire says. The founding biology comes from the world-leading labs of Dr. Rakesh Jain at Harvard/MGH and Dr. Ron Evans at the Salk Institute. Dr. Robert Langer at Harvard, who cast the model for enterprises spun from academic science, is also a founder.

Big missions, big challenges, and of course, big transformations still drive this industry explorer on to blaze new trails. Like many other industry players who have been around to see a good slice of history, she is obviously not done yet — not by a long shot.

RON COHEN
Moderator

STEVEN MILLER
Express Scripts

JEFFREY BERKOWITZ
Formerly of UnitedHealth Group/Optum

JEREMY LEVIN
Ovid Therapeutics

DAVID MEEKER
Formerly of Sanofi Genzyme

In last month's issue, we published "Can We Make Innovative Medicines Affordable? A Most Insightful Discussion On Drug Pricing — Part 1." Developed from the *Our Common Goal: Ensuring Access and Affordability of Innovative Medicines* panel discussion at the 2017 BIO International Convention in San Diego, participants include an insurance industry executive (Steven Miller, M.D., SVP and chief medical officer at Express Scripts), three biopharmaceutical industry executives (Ron Cohen, M.D., CEO of Acorda Therapeutics [session moderator], Jeremy Levin, DPhil, MB, BChir, CEO of Ovid Therapeutics, and David Meeker, M.D., former EVP of Sanofi Genzyme) and one executive who spanned biopharma, retail pharmacy, drug distribution, and insurance (Jeffrey Berkowitz, formerly EVP at Merck, Walgreens Boots Alliance, and UnitedHealth Group). We pick up where we left off with Jeffrey Berkowitz responding to a question posed by David Meeker.

Can We Make Innovative Medicines Affordable?

Concluding A Most Insightful Drug-Pricing Discussion – Part 2

ROB WRIGHT Chief Editor @RfwrightLSL

MEEKER: How do we move from where we are to a new world that allows examples like the pricing of Kevzara [an anti-IL 6 antibody launched by Regeneron and Sanofi at $39,000 per year, a price 30 percent lower than the two most widely used TNF-alpha rheumatoid arthritis drugs] to happen?

BERKOWITZ: Since we are in a world where there is 90 percent generic penetration and the fact that drugs coming to market are either second in class or highly innovative, there is an opportunity to do more creative things to get a broader value proposition. But to your point, there are perverse incentives throughout the healthcare system (e.g., wholesalers make more money when drug prices are increased, retail pharmacies tend to make less money when generic prices go up). This whole idea of a social contract [an initiative in which pharma companies have pledged not to raise prices more than a certain amount per year] on drug pricing is a little surprising. How many industries can proactively announce they are only going to take a 10 percent price increase every year and get applauded for doing so?

COHEN: But embedded in that statement of, "We're only going to take no more than 10 percent," is an assumption that for a lot of that 10 percent, their contracts are such that they are netting 3.5 or 4 to 5 percent, and the other 5 to 6 percent is going to the frictional players in the system (e.g., pharmacy benefit managers [PBMs], pharmacies, wholesalers).

MILLER: Actually, when you calculate rebates, what a biopharma gives to Medicare, Medicaid, and 340Bs are rebates. Biopharmas can blame high drug prices on a company like Express Scripts, because it is easy to blame the middleman. But biopharma is loath to point out that the government is actually taking most of the rebates. PBMs are the recipient of the rebate but are actually not the beneficiary of a lot of the rebate dollars. Express Scripts is moving to an indication-based reimbursement model to overcome the loss of existing rebates, which can happen when a new product comes to market at a lower price and without a rebate. We can't move the entire market share from one product to the new product overnight, because if we did, our insurance payers would lose an enormous amount of rebates. One of the problems with our maladapted healthcare system is a biopharma can actually bring a cheaper product to market and still have trouble getting market share.

COHEN: Earlier you gave praise to Regeneron and Sanofi for coming in at a reasonable $37,000 drug price for dupilumab. But how do we know what's expensive and what's not? Because $37,000 is still a lot of money.

MEEKER: There's no drug-pricing rule book that you can reference for determining what is a fair price for anything. We live in a world of negotiation. But to get to a negotiated understanding of what is fair requires starting early, and our early dialogue, long before approval, wasn't about the drug, but the disease. Our first goal was for everyone to understand the problem we were trying to solve. When people think about eczema, they think it is a little rash. We had to explain that we were talking about treating much more severe forms of atopic dermatitis. We went through pictures and discussions until everyone had a collective sense of how severe the disease is potentially affecting this number of patients in the United States, which brought us to the drug-price range of where we thought dupilumab should be.

> "NOW, I WILL ADMIT THAT I WAS THE CHIEF WHINING OFFICER WHEN SOVALDI CAME OUT."
>
> STEVEN MILLER
> Express Scripts

MILLER: The other thing Jeff Berkowitz and I do is look across our entire book of business and try to calculate what the total increase is going to be for our insurance plan sponsors. There are some years where you have a lot of drugs coming into the marketplace, and there is less flexibility to determine if a drug can be priced a little higher. There are other years when a drug company may be the only new entrant to the marketplace and isn't competing against much else, which allows more flexibility in our book. But PBMs aren't tasked with managing the price of one drug. We are tasked with managing the total drug spend for a plan sponsor. Insurance payers are starting to look at their specialty pharmacy spends as being different from their traditional oral-solid pharmaceutical spend. This is because they are seeing more specialty pharmacy patients, and the products these patients need are expensive and have been increasing by double digits.

BERKOWITZ: Everybody's got a forecast, and everybody's got planning, which can get blown up. For those who don't know, once a PBM's business

is sold, it only turns over every three years or so. As these are typically three-year agreements of very large populations, the value a company like Express Scripts brings to a payer or an employer is built over time. If a new revolutionary, high-priced product comes to market during one of those three years, it can totally blow up that value, company forecasts, and plans, and there is very little that can be done.

MEEKER: How should the launch and price of the Hepatitis C drug Sovaldi have been handled?

MILLER: Everyone here has been expressing the importance of talking to payers early. When it came to Sovaldi, I can't find a single payer that had been talked to prior to its launch. We at Express Scripts knew a product was coming, but we didn't know what the price of the product was going to be.

MEEKER: But if they had talked early, what would that conversation have been like?

MILLER: It would be similar to how Express Scripts worked with Regeneron and Sanofi. We would have been investigating the number of patients we could anticipate treating. What is going to be the burden to the payer? Is the payer going to be able to absorb the cost of the treatment over an annual budget? Based on that information, we would have been able to help the manufacturer determine a price that the market could bear. Now, I will admit that I was the Chief Whining Officer when Sovaldi came out. Because at $1,000 a tablet, and the fact that it was approved in December, which is after insurance plan budgets had been approved for the coming year, every one of Express Scripts' insurance plans would be in trouble. Further, I knew patients of these plans were going to be denied other therapies because of the cost of treating Hepatitis C with this new therapy. People at insurance companies were going to be losing their jobs because of Hep C. Don't get me wrong, it's a spectacular drug. As a transplant nephrologist by training, I have seen a lot of Hep C and had no success treating these patients prior to Sovaldi. The drug wasn't the problem; it was the price and the fact that we had no advance notice and weren't consulted as to what that price was going to be.

COHEN: Within the first year or so of the Sovaldi launch, UnitedHealth reported about a $100 million quarterly loss, which was almost entirely the result of not being able to anticipate the Hep C onslaught when developing its premium structure.

What if every commercial-stage biopharma company signed up for taking price increases of no more than X percent (i.e., a social contract), perhaps a percentage somewhere around that of medical inflation? Further, what if all of these companies agreed to engage with insurers, PBMs, etc., on all new drugs in their pipelines at least a year and a half before anticipated approval (i.e., listening tours)? Would that end the drug-pricing problem?

MILLER: Almost. But we also need to have a vigorous biosimilar marketplace. In the last decade, it was the generics that actually created the headroom for biopharmaceutical innovation. Here's how. Consider a patient needs to go on a new cancer drug, which is typically more "expensive" because it is new. What allowed insurers to be able to pay for these new innovations was the ability to move larger numbers of other patients over to generic treatments in a variety of other therapeutic areas. Effectively utilizing generics helped Express Scripts keeps drug spend pretty constant. Similarly, the hundreds of billions of dollars saved by the use of biosimilars will enable insurers to cover other new therapeutic innovations.

LEVIN: I agree. There cannot be a perpetual franchise for biologics. It is unconscionable for companies that have benefited from the appropriate period provided for under patent law to try to prevent the entry of a biosimilar. Rather than spend money on lawyers, they should be investing in new products to replenish their pipelines.

COHEN: What I am hearing is: Depending on the drug and the indication, it is possible for new therapies to be priced at about a million dollars per patient, and in the right circumstances, assuming there was agreement on the product's value, it could be reimbursed.

MILLER: Spark Therapeutics is working on a gene therapy for hereditary blindness. In this situation, there is no medical spend offset for such a product, because currently there is no medical treatment. So let's throw a hypothetical number out that the cost of this new treatment will be $1 million per eye. Insurers now have $2 million in completely new spend. Are plan sponsors going to be willing to pay $2 million for a treatment that might be palliative, because not all gene therapies will be curative? In the case of Spark's new product, children still can't read newsprint, but they can see better and are able to navigate around a room without an aid. As we are supposed to be in the business of providing better health for people, we are going to have to figure out how to pay for such a treatment, which means cutting out every ounce of waste

in the system to have available dollars. There will be other gene therapies (e.g., hemophilia) where we are paying $150,000 to $200,000 a person. Even at a price of $2 million, there's going to be ROI. If the hemophilia product was the first gene therapy product to come to the market, it would be a much easier argument. But it looks as if Spark's eye treatment will be the first gene therapy to market (probably this year), and though the population that will be served is tiny, we still don't have a healthcare system designed to pay for it. I think the price will be justified, and big payers should be able to figure it out. However, for small, regional health plans, it could be very challenging, especially if they have a family with multiple kids needing treatment.

COHEN: Where do we go from here?

BERKOWITZ: The concept of value-based contracting around therapeutic classes is getting simpler, because there are even fewer opportunities as we continue to solve problems on the edges. However, do we have the necessary skillsets? For example, it has traditionally been the lawyers who have done all the negotiations on rebate-oriented contracts. Yet now we are asking these same lawyers to sit in a room with really creative scientists solving really meaty problems around diverse pieces of data in a fragmented system. These lawyers don't have the skillsets necessary to support a completely new contracting construct.

LEVIN: In addition, it is not just a matter of bridging the gap between scientists and lawyers to help with value-based contracting: the legal system also inhibits in some cases the various elements of a healthcare system from working together better. There are very clear regulations about who can talk to whom, when, and what they can and cannot talk about. We need to take a hard look at some of these regulations. For example, it is very difficult for CEOs of multiple sclerosis-oriented companies to sit together alone in the same room without lawyers. And they certainly cannot have a discussion on the current MS pricing system. I imagine it to be very difficult for insurers and PBMs to function in a "column" discussion with one company on one drug without looking to ensure that all companies with a similar drug are included at that table.

MILLER: Let's have a moment of truth. You three (Cohen, Levin, and Meeker) do not represent biopharma, as you have been involved in these discussions repeatedly, while many of your colleagues avoid these conversations. As such, the vast majority of industry is not where we are [on this panel] today, and this includes payers. Most of the people doing contracting for payers, including my company, are trained to beat the ever-living daylights out of the pharmaceutical manufacturers.

BERKOWITZ: That's why I call what we are seeing with "value-based pricing" as being a box-checking exercise. For when you look into what companies are really doing when they announce the development of an intrinsic value-based contract, it often involves a very small population or is a piloted program.

LEVIN: Jeff Berkowitz and I have gone to battle negotiating over generic contracts. And while it was all very polite, it was still a battle about dollars and cents — it's really a commodity discussion. I don't think we (Cohen, myself, and Meeker) are in that business, and we need to develop, as Jeff says, a far deeper understanding of value-based contracts for branded medicines. But I think we all understand that in the absence of true focus and change within industry on this issue, regulators and policymakers may implement forms of pricing control that will be catastrophic in its complexity and distance from a robust value-based pricing system.

COHEN: At this moment there is legislation being proposed that would allow for the reimportation of drugs to the United States. As other countries allow for government-developed price controls, the United States would essentially be importing these price controls. This spearheads the way for the federal government to negotiate/set the price — which, as we all know, isn't much of a negotiation. In addition, counterfeit drugs are a major source of revenue for certain terrorist groups, so we need to think about that when considering reimportation.

MEEKER: We have to be patient, because the reality is this is not going to change overnight. When we talk about self-regulation on the part of the industry, there isn't going to be a pact where every company agrees to sign up. But there will be companies that lead by example, and slowly more companies will get on board, because we all have a vested interest in the system's success, and if it breaks, we all lose. Secondly, I want to be rewarded for innovation that solves a problem, and then be able to get that solution to everybody who needs it. But to compete in that world, I don't want to be stuck trying to navigate contracts that are in place for three to four years, for those won't allow me to get the volume needed.

LEVIN: If reimportation of drugs is allowed,

we need to understand that the FDA does not have the funding and the manpower to adequately review the integrity of the supply chain and quality of these "reimported" drugs or all the sources from which they come. Some estimate that the majority of the drugs in the Middle East and Africa are fakes or counterfeit. America's custody chain of getting a drug from the manufacturer to the patient is robust and largely managed better than most of the world. To safely reimport drugs would require significant investment in FDA infrastructure, manpower, and substantially increased inter-agency international agreement and cooperation.

BERKOWITZ: The United States has 90 percent generic penetration. Three manufacturers represent 50 percent of the U.S. volume of generic distribution. You have four buyers that represent 95 percent of all generic purchases in the United States. And yet, in the U.S., even for highly commoditized drugs, the prices for generics are higher here than anywhere else in the world.

LEVIN: Innovation in the generic industry should be in developing new low-cost manufacturing capabilities.

COHEN: To Steve Miller's earlier point on biosimilars, biopharma's value proposition of funding innovation through high prices for a limited exclusivity period depends on having a robust genericization process, which includes biosimilars.

Now, David Meeker mentioned earlier that drugs have been steady at about 14 percent of total healthcare spend. But as we get into developing more curative drugs, we will be replacing procedures and some of the requirements for provider care. As such, we can anticipate more drugs taking over a larger share of healthcare spend. But unfortunately, health insurance plans aren't currently structured to accommodate such a scenario. So what do we do?

MILLER: There are a number of stakeholders who need to work toward changing the system, including payers. High-deductible plans do not work, because very few families in the United States have $2,000 in the bank. Most people who buy a high-deductible plan are essentially playing roulette that no one in their family is going to get sick. We have got to make changes to these plans and put in guardrails so the maximum out of pocket for any prescription is, for example, $250, as we have a lot of data indicating nonadherence to medication skyrockets when the out-of-pocket expense surpasses $250.

BERKOWITZ: We are not going to solve any of these issues if we continue to have biopharma, large pharma, PBMs, retail pharmacy, drug distributors, and payers continuing to operate in a vacuum. We need a forum where these groups can come together.

COHEN: There is the Council For Affordable Health Coverage, and its members include Aetna, BIO, Cigna, CVS Health, Express Scripts, GSK, and Sanofi, just to name a few.

MILLER: Express Scripts has not found that particular coalition to be very useful, as it is mainly an advertising coalition. It was supposed to have a public relations campaign and was not intended to assist with driving healthcare policy change. There are a lot of coalitions out there, all have agendas, and many are often fronts for different organizations.

BERKOWITZ: It goes back to the beginning of taking the time to engage early. I'm often surprised at how many senior-level biopharmaceutical executives will fly at a moment's notice to the Czech Republic to do a business review for that country, but have never visited Humana, a company which probably represents somewhere between 5 and 15 percent of their company's total dollars.

MILLER: The reason we have had a difference at Express Scripts in working with Regeneron and Sanofi is because we are now engaging the highest level of our company with the highest level of their companies. In the past, executives on both sides delegated this engagement to someone else. Here's some advice: The people biopharma companies get to come to AdComms on the payer's side are not the decision makers. Neither Jeff [Berkowitz] nor I go to AdComm meetings, yet we are the ones who make the decisions. The people you are getting to come to these meetings are some midlevel physicians or other person who actually does denials or utilization management, and you could make better use of your resources.

COHEN: I'd like to offer a concluding thought. It is up to us (i.e., employees of the healthcare industry) to reach out to the senior levels of our organizations to get change to happen in a constructive way. Because in the end, it is all about the patient, for we are all patients, too.

For additional insights on drug pricing, be sure to check out our special drug pricing roundtable published in Life Science Leader's *July 2016 issue.*

Will Value-Based Drug Pricing Work?

Part II

CAMILLE MOJICA REY Contributing Writer @CamilleReyATX

This is the second in a two-part series on value-based healthcare. In Part I, Life Science Leader *explored the role of the pharmaceutical industry in the shift toward value-based healthcare.*

In August 2017, the FDA announced the approval of the first-ever gene therapy treatment. Novartis' Kymriah was created to treat children and young adults with an aggressive form of leukemia called B-cell acute lymphoblastic leukemia, whose cancer has resisted standard therapies or who have relapsed. The treatment is unique in that it trains the patient's cells to attack the cancer, but it is also the first-ever cancer treatment to come with a money-back guarantee. If the patient does not respond to the one-time $475,000 treatment within one month, there will be no payment to Novartis. This makes Kymriah a test case not just for the commercialization of gene therapy, but also for value- or outcomes-based payment models and arrangements.

"This is a step forward," says Shefali Shah, an industry consultant who helps pharmaceutical companies price their drugs. Shah, who did not work with Novartis, says many of her clients are considering value-based payment arrangements. Supporters of moving the entire healthcare system to value-based pricing hope that these kinds of payment arrangements will create win-win situations for patients, payers, and companies that make life-saving drugs and treatments. The ultimate goal of value-based care is to bring down the cost of healthcare while rewarding innovation. What remains to be seen is whether value-based models will be applied on an industrywide basis, and, if so, will that bring down the cost of prescription drugs? Regardless, experimentation on the part of drug companies with value-based models has begun, largely in response to public outrage over the cost of prescription drugs and the U.S. government's efforts to rein in those costs using value-based payment arrangements for healthcare providers.

The big question most industry experts have when it comes to the use of value-based models is: "What's in it for pharma?" People view these models as being inherently fair. They don't want to pay for something that doesn't work. A "money-back" policy promotes trust. According to Shah, companies like Novartis who enter into value-based payment agreements are letting patients know they are "committed to them." It's also true that cost can get in the way of building a client base. Shah points out that many people who go into drug development do so because they are interested in the science of healing and potential for advancing patient care. "The leaders of some of these companies want to give the science a chance to succeed without being weighed down by cost." This is already evidenced by the millions of dollars worth of drugs the industry gives away at little or no cost to those who cannot afford them. It also cannot be ignored that offering to give money back if a drug doesn't work is just good PR. In the case of Kymriah, the value-based payment agreement helped to relieve some of the sticker shock experienced by patients and the general public when the approval was announced.

OBSTACLES TO VALUE-BASED DRUG PRICING

Currently, there are both logistical and social obstacles to the adoption of value-based models for drug pricing. The biggest obstacle at the moment, according to Shah, is the federal government's current reimbursement system. The pricing of Kymriah, though steep, is fairly straightforward. "From a reimbursement standpoint, Kymriah doesn't have a lot of the challenges other therapies would," Shah says. That's because Kymriah is administered on an inpatient basis. Drug reimbursement rates for inpatients are not based on average

sales price, or ASP. So, having to give away some free of charge will not affect a measure that determines reimbursement to the hospital or physician. Also, because it is approved for a young demographic, Medicare is not involved. Medicaid's Best Price (BP) applies to covered outpatient drugs, a definition which can vary from state from state but may provide the path to avoiding BP implications for Kymriah. "This is important because ASP and BP are considered some of the key barriers to indication-based pricing and outcomes-based payment for drugs that are used primarily in the outpatient setting and in older patient populations," Shah says.

Another barrier to value-based pricing payment agreements is the way Medicare reimburses insurers for different types of drugs. Within Medicare, if you have a drug that is an oral, it is covered under Part D. Drugs delivered intravenously are covered under Part B. "Under Part D, there is far more pricing flexibility because the drugs are not priced on a per-milligram basis. You can have a 10- or 15-milligram pill that costs $10. The insurer doesn't pay more for higher doses," Shah says. So, patients with different dosage needs could pay the same amount. Under Part B, insurers and physicians are reimbursed on a unit price or per-milligram basis. Because some patients need higher doses, reimbursement calculations are thrown off. One possible fix for the problem is if drugs could be given multiple reimbursement codes. For example, if the dosage of a particular drug for the treatment of colon cancer is half of that for the treatment of breast cancer, diagnosis-specific codes would allow for these patients to pay the same for treatment with the same drug. "The big losers of offering indication-based pricing within the current system are these manufacturers and doctors," says Shah. "Who wins? Insurers. The savings are not passed to the patient. Until some aspects of the Part B side of Medicare are fixed, it's going to be very hard to adopt value-based models."

Critics of value-based models maintain that, until the federal government changes the reimbursement system, many companies will not feel the pressure necessary to develop innovative value-based payment agreements. For David Howard, the question is one of motivation: "Why would a drug company rearrange their pricing to lower their profits?" Howard is a professor in the Department of Health and Policy Management at Emory University. He also questions whether these models would really bring down drug costs. "The price for a patient who does not get a benefit goes down, but the price for those for whom it works goes up. It seems it could be kind of a wash." Howard also says that the administrative complexity required to implement a value-based pricing model would be prohibitive. "It's hard enough for hospitals to track the outcomes of their patients, let alone drug companies writing tracking into their payment contracts."

"The leaders of some of these companies want to give the science a chance to succeed without being weighed down by cost."

SHEFALI SHAH
Pharma Industry Consultant

Other critics question the premise that the implementation of value-based models will result in lower prices. "Value does not inherently require lower cost," says Louis Jacques, M.D., senior VP and chief clinical officer for industry consulting firm ADVI. "A focus on value could increase costs if there is a larger incremental increase in value as reflected in improved clinical outcomes for patients." That said, Jacques says he sees inertia as the main barrier to the widespread implementation of value-based payment agreements. "People tend to be risk-averse in healthcare payment policy and see comfort in a known paradigm, even as they complain about its failings." Likewise, the call for lower-priced drugs is, in part, due to a complicated healthcare payment system; most people don't actually know the real cost of the drugs they take. "The public conversation on value focuses on healthcare because the ultimate consumer is insulated from the true cost of the purchase. We don't seem to have similar public debates on the value of flat screen TVs or OTC drugs. I think that is because the marketplace accurately reflects value choices made directly by consumers. Arguably, the ongoing insulation suggests this will remain a challenge well into the future."

HOW TO PREPARE

Like Shah, many industry leaders believe they see the writing on the proverbial wall: The U.S. healthcare system is already moving in the direction of value-based care. (*See Part I of this series.*) It's only a matter of time, they believe, before the federal government begins to use these models as well. These leaders are already hiring pricing experts who are well-versed in value-based models. They are already thinking about ways to measure the value of their products and price accordingly. Shah says there are many ways to prepare for the shift to value-based pricing and, for those who see the value in using these models for themselves now, tips for success. First is starting the conversation around value and pricing early in the drug development process. "It is important for the industry to be thinking about the value that the drugs they deliver have as they are developing them," Shah says. Large companies may have the expertise in-house, but midsize and small companies often do not. That is a problem the industry will have to address. "It is a complicated process. You need to have a value-based expert involved in the earliest stages. During Phase 2 is the best time. A lot of pivotal decisions are made during this phase that cannot be undone," Shah explains.

"Value is demonstrated in head-to-head comparisons whether we are talking about drugs or automobiles. I think the automobile market has benefited from having trusted third parties do these comparisons, looking at factors that buyers consider as contributing to value (e.g., occupant protection in crashes, frequency of repair, load-carrying capacity, fuel economy). As we amass more therapeutic options even in just the biopharmaceutical space, it is a challenge to determine which choices bring the best value for individual patients in real-world settings."

NEEDED CHANGES

The current government reimbursement systems remain the largest obstacle to the implementation of value-based models. Until these models become widely adopted, there are other ways to lower the cost of prescription drugs. One way, says Emory's Howard, is to change the approval process for biosimilars. "A new pathway for approval of generics of biologics that are not exact copies would be one of the best ways to lower drug prices and encourage patients and physicians to adopt biosimilars," states Howard.

Changes on the part of insurers and physicians could also bring down drug prices, Howard says. "Insurers and physicians should be more willing to push back on drugs that don't give a lot of benefit. The healthcare system has shown a high degree of willingness to adopt new treatments regardless of how high the benefit or the cost. As a result, that gives drug companies a lot of pricing power. So if physicians were not so quick to adopt drugs with marginal benefit, drug companies would have to do more to compete on price."

> *"It's hard enough for hospitals to track the outcomes of their patients, let alone drug companies writing tracking into their payment contracts."*
>
> **DAVID HOWARD**
> Professor, Department of Health and Policy Management, Emory University

Shah adds that working early with payers is also important. Novartis, for example, would have had to be working closely with the CMS to have announced the value-based payment arrangement on the same day FDA approval was announced. That's the way to do it, Shah says. "It makes sense for companies to be working closely with CMS, other payers, and the FDA simultaneously." Companies need to be thinking about value-based payment models in parallel with the clinical trials process. "It's much easier to come up with a value-based price, especially for high-value treatments that bring significant value to patient care, before a drug hits the market."

ADVI's Jacques says pharmaceutical companies will have to learn to trust third-party evaluations of their products if a value-based system is to become a reality.

Whether value-based models continue to grow in popularity remains to be seen. "I think value-based pricing could be a step in the right direction, but likely will not solve every potential issue as medicine continues to advance," Shah says. "As treatments become increasingly personalized, it will be harder to use one-size-fits-all payment models and the bundling of services favored by proponents of value-based healthcare delivery."

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Don't Have A Chief Innovation Officer? Get One ... Now

GAIL DUTTON Contributing Writer @GailLdutton

Chief innovation officers (CInOs) are poised to become one of the more important executives in the C-suite in pharma just as they are in other industries. As the scope and pace of changes facing the life sciences industry accelerate, innovation must occur faster — not just in R&D but throughout the organization. Achieving fast, focused innovation, however, often requires thinking outside the usual silos and chains of command to foster — and manage — innovation in unusual ways.

EVERY COMPANY NEEDS A FLOATING VISIONARY

CInOs are their company's chief visionary. Not responsible to individual business units, they have the freedom to watch trends in their industry and in others, and the responsibility to understand open innovation, suggest new ideas and business models, seek out new technologies and new methodologies, remove roadblocks, and help teams go from "Can we do it?" to "How can we do it?" Their role is to inspire staff members to develop disruptive strategies and products.

Plenty of companies have innovation officers for key business units. Fewer have them for the company as a whole. CInOs are particularly sparse in Big Pharma. Yet having someone who regularly reaches across silos to share ideas, ask the "what if" questions, and matchmake among programs can catalyze innovation in ways business unit innovation officers often can't.

CINO OF MANY HATS – STARTUPS

Innovation may be easiest at startups. "Cloud Pharmaceuticals is an early-stage company, so we don't follow industry conventions," says Ed Addision, the company's chairman and CEO. "Rather than draw an organizational chart and find people to fill it, we find good people who can contribute and then create their boxes. We recruit people with a moonshot mindset."

Cofounder Lawrence Husick fills the CInO box as well as that of in-house counsel. "He's not the kind of guy to design and develop products, and he's not a regular operations guy. He's more strategic," Addison says. Perhaps most importantly, Husick, who teaches Management of Innovation at Johns Hopkins University, knows that innovation can be taught.

"We are a small company, so the only barriers to innovation are attitude, feasibility, and capital," Addison says. It helps that Cloud Pharmaceuticals is unencumbered by the large bureaucracy common in many older, larger organizations.

> *"Creative thinking coupled with pragmatic skepticism in an entrepreneurial setting is crucial to making this approach work."*
>
> **DAVID STEINBERG**
> Cofounder and CInO, PureTech Health

In practice, this means that Cloud Pharmaceutical's chief scientific officer guides scientific innovation in its drug discovery work while the CInO takes a broader look at innovation. Husick brings in new technologies for consideration and inspires and motivates staff. "They play different roles," Addison says.

For instance, Husick identified blockchain technology — a new, secure way to verify and audit transactions — as

a potential technological method of tracking IP rights. "We plan to use it once we increase our volume of projects," Addison says. Another example is the IP strategy Husick is developing to market many of the targets discovered by artificial intelligence during the company's probes of the entire drugable genome. To handle the considerable computation needs, Cloud Pharmaceuticals is contracting with a data center in Iceland and, in the process, launching a new business model in which it sells data to pharmaceutical companies.

ENVISIONING THE FUTURE – MIDSIZE COMPANIES

PureTech Health calls itself "the biopharma company of the future." To live up to that bold claim, it has to innovate as a matter of course. It created the CInO position to help guide and stimulate innovation throughout each aspect of its programs.

"I'm responsible for 'what's next' at PureTech Health," says David Steinberg, cofounder and CInO. Envisioning what's next involves working closely with PureTech's internal scientists and with a broad network of academic labs and companies throughout the world. In so doing, Steinberg tries to remain at the forefront of emerging fields of biology and current thinking so he may "think creatively and holistically about potentially disruptive 'next' opportunities." Such broad, interdisciplinary exposure helps catalyze insights that set the theme for new areas of discovery that lead to first-in-class solutions to major health challenges.

Steinberg has two fundamental approaches to innovation. First, he and his team of internal and academic collaborators identify problems in search of solutions (rather than developing a technology and wondering where it could be applied). Once probable solutions are identified, he says, "My job then is to de-risk or shut down experimental programs early on so each new program has the best chance of reaching an informative clinical outcome. It's a very nimble and entrepreneurial approach that can yield results with only the right team. And it only can be accomplished proactively and collaboratively." The company has used this approach for each of its 22 programs, seven of which are in the clinic.

J&J'S NEXT BIG THING

Johnson & Johnson doesn't have a CInO but, in January 2018, William N. Hait, M.D., Ph.D., will take the reins as the first-ever

global head of Johnson & Johnson external innovation. This new position covers all of J&J, including its pharmaceutical, device, and consumer products divisions.

"At J&J, we felt we had advantages that could be realized if consumer, medical devices, and pharmaceutical divisions could be harnessed to work together," Hait says.

"We think of innovation as an energy grid, with clusters of innovation like those in San Francisco, Cambridge, London, and Shanghai [sites of J&J innovation centers]," he elaborates. "To take advantage of those innovations, you must be plugged into the grid. Someone must take the lead in plugging in and drawing innovations from that grid in a focused, sensible way."

When Hait transitions from global head of Janssen R&D to global head of J&J external innovation, he will lead R&D initiatives across J&J's innovation centers, JLABS, venture funds, and the World Without Disease initiative. His mission, he says, is to "take on problems that less broadly based companies would have difficulty tackling."

Creating a world without lung cancer is one example. Oncology products today typically focus on extending remission rates, but "to be curative, you need a group totally focused on cures."

To create those focused groups, Hait plans to tap the expertise of behavioral scientists in the consumer group who understand branding, engineers who know how to design a range of devices, and scientists who know how to make drugs. "Put them around a table, and it may be possible to cure or prevent a disease."

J&J isn't creating a new bureaucracy. Instead, Hait will work autonomously, collaborating with core business units and external partners. He envisions a research group heavily involved in licensing and partnering that is closely connected to core elements across J&J. "The critical role is to see the possibilities that others may or may not see and to invest to bring them to the point where those possibilities are actionable," he says.

DREAM BIG, BE EXCITING

Stimulating and guiding innovation begins with a compelling strategy. "The notion of creating a world without disease seems ridiculous," Hait says. "But, if you have a compelling strategy, people begin to believe it may be possible. Then it becomes self-organizing." As J&J fleshed out its approach, employees from throughout the world called and asked to be a part of it.

Be collaborative. Bringing together diverse disciplines and roles sometimes yields surprising insights into the problem as well as the solution. PureTech Health, for example, consults its commercial group in addition to its internal and external medical and scientific experts. "Creative thinking coupled with pragmatic skepticism in an entrepreneurial setting is crucial to making this approach work," Steinberg says.

"We are a small company, so the only barriers to innovation are attitude, feasibility, and capital."

ED ADDISION
Chairman & CEO, Cloud Pharmaceuticals

UNLEASH THE RISK-TAKERS

"Bring me maniacs willing to go all out, because these things aren't easy to accomplish," Hait says. He wants risk-takers who can see the possibilities of the mission and are willing to build a new structure, eschewing the sometimes stifling comfort of tried-and-true models and methodologies.

"An entrepreneurial culture that balances creativity with skepticism is vital," Steinberg agrees. "The same innovative process that works in a small or mid-size firm won't necessarily work in a larger company [despite greater resources] if that entrepreneurial culture is lacking."

ENGAGE THE C-SUITE

Not surprisingly, C-suite buy-in is imperative. That means gaining not just nodding acquiescence but the informed support that comes from reporting directly to the C-suite.

The CInOs at Cloud Pharmaceuticals and PureTech Health both are core members of the senior executive leadership teams. At J&J, the reporting lines are still being defined, but Hait is likely to continue reporting directly to the CSO and to have direct relationships with others on the senior executive committee. These direct relationships enable them to make timely contributions to the direction of the company that both bolster and focus innovation.

As innovation transitions from a hit-or-miss endeavour to a process that can be directed and managed, the case for a CInO is growing. A proactive chief innovation officer can provide the guidance for enterprise-wide creativity, while enhancing an atmosphere that encourages innovations that match the company's goals and mission.

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Pet Medicines: Smaller Market, Lower Costs, Greater Margins

ED MISETA Chief Editor, Clinical Leader @EdClinical

Making the move from a pharmaceutical firm to an animal health company might seem like taking a small step from one drug discovery organization to another. But that transition process for one executive was a bigger challenge than he expected, and now it has him looking at the drug discovery process in a new way.

After receiving his doctorate from Harvard Medical School, Richard Chin began his pharma career by serving as medical director at P&G Pharmaceuticals. That was followed by stints at Genentech, Elan Pharmaceuticals, Oxigene, and a few other firms working on drugs for arthritis, asthma, and eye diseases. But as an animal lover, Chin was always thinking about ways in which he could use his pharma experience to improve the lives of pets.

Chin first met Denise Bevers while both were working at Elan. They quickly discovered their mutual interest in the health of animals. "After discussing the opportunities that existed in the area of animal health, we considered starting a veterinary company," says Chin. "Unfortunately, we did not have a breakthrough idea at that time, so the idea was put on hold."

FROM ANIMALS TO HUMANS, AND HUMANS TO ANIMALS

Chin eventually moved on to other companies, later landing at an organization called the Institute for OneWorldHealth. OneWorldHealth, funded primarily by the Bill and Melinda Gates Foundation, develops low-cost drugs for impoverished patients in developing nations. While leading that organization, Chin realized that many of the drugs used on patients in third-world countries had originated with drugs developed for livestock. That led him to wonder if drugs developed for humans could be used on animals. "Pharma companies have spent billions of dollars developing drugs for humans that are not available for animals. Many were for human diseases that I knew also existed in animals, such as diabetes, osteoarthritis, lupus, inflammatory bowel disease, and various forms of cancer. The diseases also tend to be similar in humans and animals. That was the genesis of our company."

Chin reconnected with Bevers, and together they cofounded KindredBio, where he is now the CEO and she serves as COO.

"This is a new field, and it almost feels weird to call it new considering how long humans have had animals as pets," says Chin. "But one trend that is relatively new is the idea of pets being looked at as members of the family. That trend has been in existence for only the last 15 or 20 years. Today, people spend more on pets than ever before and will search for medicines to cure their diseases, just like we do for humans."

> *"We have not seen the price escalation that has occurred in clinical trials for human drugs."*
>
> **RICHARD CHIN**
> CEO, KindredBio

AN OPPORTUNITY AND A CHALLENGE

Although animal health is a burgeoning market, Chin and Bevers found the newness of it to be a challenge when launching the company. "Investors understand

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Zimeta (dipyrone oral gel)	Fever in horses
KIND-014*	Equine gastric ulcers
KIND-015	Metabolic syndrome in horses

* KindredBio also has 10 biologic product candidates.

the pharma industry," says Chin. "They understand human diseases, and they understand the process of getting a new drug approved and commercialized. But when it comes to animal health, it's a different story. When I first starting talking to them, I found they didn't understand the regulatory pathway for animal medicines and didn't understand what the market for these drugs looked like. That required us to do some educating on these medicines."

They would explain that the market size is 10 times smaller for animal medicines than it is for humans. They also would note that a $100 million drug is considered a blockbuster in animal medicine. But the flip side of that is that the cost of developing animal medicines is 100 times less than for humans. "A new animal drug can be developed for $5 million or less, whereas the cost of developing a new drug for humans can be $1 billion or more," he says. "There are also far fewer companies producing medicines for animals."

HUGE SAVINGS ON TRIALS

When developing a new drug for humans, clinical trials are a huge cost-driver. On the animal side, it is also the area where a large portion of the savings is accrued. First, the studies are much smaller. Rather than performing two Phase 3 studies that include thousands of human patients, veterinary studies require only one pivotal study and a minimum of 100 animals exposed to the drug. The per-animal cost is also a lot lower than the cost of including a human in a trial, and the trials tend to be shorter. According to Chin, the maximum length of a study is around six months, but many will be complete in less than 30 days.

"In human drug development, it is not unusual to spend between $50,000 and $100,000 per patient participating in a trial," states Chin. "In the veterinary medicines field, the cost is around $5,000 per patient. The studies are shorter, the cost of veterinarians tends to be less than the cost of a human physician, and we have not seen the price escalation that has occurred in clinical trials for human drugs."

Chin notes that 20 years ago, pharma companies could still conduct a human trial for $5 million to $10 million. "Today you can't perform one for anywhere near that price. With animal medicines, you still can. Many Phase 3 studies are generally performed at a cost of less than $1 million."

The field of animal medicines could include both family pets and livestock. When starting the business, Chin and Bevers opted to focus on family pets and horses (which are also close companions to their owners). As Chin explains, livestock is a very different market than pets. Even though both involve animals, the drugs are very different.

In the pet market, drugs are developed to treat therapeutic diseases, just like in humans. With livestock, most of the drugs on the market are vaccines, antibiotics, and hormones that speed growth in animals. That drug business is high-volume and low-margin, which is not the market Chin wanted to enter. "Our expertise lies in treating diseases," he says. "That is no longer a growth area in livestock."

A SIMILAR REGULATORY PATHWAY

In the area of pet medicines, Chin estimates more than 80 percent of therapeutics are regulated by the FDA (topical treatments such as flea drops are regulated by the EPA). For that reason, the regulatory pathway is similar to what it is for new human medicines. A randomized, controlled study must be used to show that a new drug is both effective and safe.

"If we develop a drug to treat dermatitis in canines, we would find dogs that have the condition," notes Chin. "The veterinary clinics participating in the study would be provided with the protocol and the medicine. Sites are monitored in a manner similar to clinics taking part in a human study. With animals, informed consent is obtained from the owner of the pet, and there are inclusion and exclusion criteria that must be met. Dogs selected for participation will then be randomized and receive the drug."

One thing that KindredBio is able to cut out of their discovery process, which further reduces their development costs, is rodent studies. The reason for this is that any drugs they test on animals are coming from pharma companies developing treatments for humans.

"These drugs have already been tested on animals for safety and efficacy before ever being used in humans," adds Chin. "In fact, I like to joke that humans are the preclinical species on which medicines are tested before being administered to pets. Our clients and veterinarians seem to get a good laugh out of that."

The Impact Of CETA On The Pharmaceutical Industry

YAZAN SALEH

The Comprehensive Economic and Trade Agreement (CETA) is a free-trade agreement signed between Canada and the EU at the end of 2016. Described by the Canadian government as "one of the most ambitious trade initiatives," the scope of the agreement extends across all sectors of the economy from agriculture to healthcare to pharmaceuticals.

For Canadian businesses, the agreement will reduce trade barriers for access to Canada's second-largest trading partner and the world's second-largest economy. Similarly, European companies will enjoy opportunities for growth in Canada because of improved regulations and access to new market sectors. Overall, CETA will eliminate 99 percent of all tariffs between the trading partners upon signing, with the remaining 1 percent of tariffs to be eliminated over the next three to seven years. The impact of CETA on the life sciences industry is rooted in regulatory changes surrounding IP protection and government procurement as described below.

PATENT TERM RESTORATION

The level of IP protection in Canada has traditionally been a concern for multinational corporations (MNCs) as evidenced by consistent inclusion as a "Watch List Country" on the USTR (Office of the United States Trade Representative) Special 301 Report and its corresponding PhRMA submission. Prior to the signing of CETA, Canada was the only G7 country that did not incorporate any patent-term-restoration provisions in its legislation. As a result, some of the market exclusivity period for pharmaceutical products was lost while patentees were awaiting regulatory approval. Once ratified, CETA will help address this issue by allowing patentees to extend their patent terms for a certain duration depending on how long Health Canada's approval takes. The exact length of the restoration period will be calculated by subtracting five from the period between the patent filing date and the marketing approval date (i.e., Notice of Compliance [NOC] date). Patent-term restoration, which is officially referred to in Canada as a certificate of supplementary protection (CSP), will not be retroactively available to already-approved products and will be capped at a maximum of two years. When compared to other countries, this cap falls short as EU countries allow patent-term restoration of up to five years. Nevertheless, the policy is a step in the right direction for the industry, as it will help recover some of the time lost from the 20-year term of a pharmaceutical patent.

RIGHT TO APPEAL

Patent linkage regulations in Canada require that generic (and biosimilar) manufacturers issue a notice of allegation (NOA) document to patent holders when seeking marketing approval for their generic products. The NOA should describe noninfringement of all the relevant patents or demonstrate how the patents are invalid if the generic company is making such a claim. The patentee would then have a 45-day period to decide whether to take action against the marketing of the generic product through the Federal Court of Canada. Overall, a 24-month stay period will begin when the patent holder initiates such an action. During this stay period, the Minister of Health may not issue an NOC to the generic company unless the federal court finds that the parties involved in the challenge were not acting with due diligence. The federal court decisions regarding the challenge could previously be appealed by the

generic company but not by the patentee. CETA will give both the challenger and the patentee equal appeal rights, thus allowing court decisions to be potentially reversed regardless of the initial outcomes.

GOVERNMENT PROCUREMENT

Under CETA, Canadian and EU governments will allow businesses from any of the signatory countries to place bids on public tenders. Policies that favor local companies and products are to be eliminated, thus putting foreign companies on a level playing field with their domestic counterparts. A significant growth opportunity exists as European and Canadian government procurement markets amount to more than $2.6 trillion and $100 billion respectively. Most importantly, CETA will open up tenders to foreign businesses at the subnational level, thus allowing EU companies to place bids on provincial and municipal tenders in Canada (and vice versa). This change is particularly relevant to the healthcare and pharmaceutical sectors, as procurement of medications in Canada is largely conducted at the subprovincial level. Pharmaceutical manufacturers and suppliers will face some challenges in navigating the fragmented procurement system of each province. Nevertheless, direct access to hospital-level and regional public procurement agencies is undoubtedly an untapped market for foreign pharmaceutical manufacturers.

"The impact of CETA on the life sciences industry is rooted in regulatory changes surrounding IP protection and government procurement."

IMPLEMENTATION TIME FRAME

In Canada, Bill C30 (Canada-European Union Comprehensive Economic and Trade Agreement Implementation Act) received royal assent to become law in May 2017. The Canadian government has since begun publishing the impending regulatory changes for a public review process. In the EU, implementation of trade agreements generally depends on whether the union has exclusive competence or shared competence. Exclusive competence means that the executive arm of the EU, also known as the European Commission, can finalize the agreement solely. On the other hand, shared competence requires that both the European Commission and the individual European governments must approve and finalize the agreement prior to implementation. CETA has been introduced as a mixed- type agreement whereby the EU has exclusive competence for some provisions and shared competence for others. Since the EU approved CETA in May, exclusive-competence provisions, which account for over 90 percent of the provisions in CETA, will come into effect without requiring specific EU-member-state approval. According to a statement released by the Canadian Prime Minister and the President of EU Commission, and by the time this article goes to print, CETA provisional approval will have begun on Sept. 21, 2017. Provisions that require individual member states' approval include those covering investment protection and the formation of the investment court system. As of September 2017, five EU countries — Croatia, Czech Republic, Denmark, Latvia, and Spain — have approved the agreement at their respective parliaments.

RECOMMENDATIONS FOR THE INDUSTRY

Innovator companies choosing to challenge generic manufacturers for infringement must act with due diligence as they could be held liable for delaying generic entry. For example, if the patent detailed in the NOA is deemed invalid by the Court of Canada, the generic manufacturer can seek compensation from the patentee for lost revenue for the period that begins on the date of the challenge. Particularly important is that the end date of the period for which damages can be claimed is no longer specified in the regulations. In other words, generic companies can try to argue for "future damages" that extend beyond the date that the final court decision is made. In light of the potential for increased damages, innovator companies should consider the option to avoid any liability by renouncing the 24-month stay period. In such a case, a generic product would be eligible to receive market authorization in the interim while the patentee could continue to pursue action for infringement.

In addition, companies seeking to acquire patent-term restoration in Canada should take extra note of the eligibility criteria for filing for CSP. According to the amended Patent Act, a manufacturer must file a CSP application within 18 months of filing marketing approval in any of the following international jurisdictions: Australia, EU (and any member country), Japan, Switzerland, or USA. Therefore, MNCs must ensure coordination in their international drug submissions to maintain eligibility for patent-term restoration in Canada. This deadline is set to become more restrictive one year after the implementation of CETA, as the 18-month time period is to be reduced to 12 months.

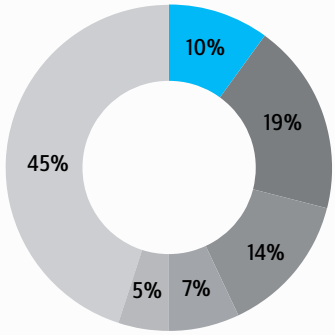
Strengthening communication and work-sharing between the different market-access teams of a multinational manufacturer will be imperative to successfully meeting the deadlines for CSP applications.

MNCs should consider taking advantage of the enhanced IP protection in Canada by boosting investment in manufacturing and research & development activities. Canada's attractiveness for pharmaceutical manufacturers is further highlighted by having the lowest business costs across the G7 countries for biomedical research and development. A significant opportunity for growth exists, considering that Europe is currently Canada's second-largest export market for pharmaceutical products ($1.04 billion in 2016). Since many of the changes brought about by CETA are regulatory changes made to federal laws, life sciences companies outside of Europe also will benefit indirectly from CETA. For example, patent-term restoration provisions will be applicable to all pharmaceutical manufacturers regardless of their geographic locale.

OVERALL IMPACT AND CONCLUSION

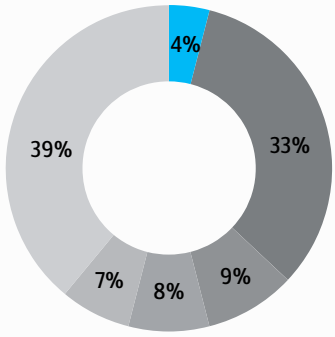
CETA is estimated to boost total trade between Canada and the EU from $71.4 billion to $85.68 billion. For life sciences companies, the new appeal rights and patent-term-restoration provisions will offer innovator companies increased protection against generic competition, which could potentially improve market share and boost revenue. On the other hand, provincial governments in Canada, which are largely responsible for funding reimbursed drugs, could face increased financial pressures because of the higher prices of patented drugs. For the industry, this can lead to negative consequences as provincial governments may be forced to omit coverage for new innovative therapies because of cost constraints. To help allay such fears, soon after signing CETA, the federal government of Canada noted that shifting expenses inappropriately onto the subnational government is not the intent, indicating that they would discuss the "cost of CETA" with the provinces at the appropriate time. It has been proposed that the federal government might consider providing some financial assistance to the provinces to help offset any unintended costs of CETA. Interestingly, the provisional implementation of CETA comes around the same time when the U.K. might begin proceedings to leave the single EU market. With the U.K. being Canada's third-largest trading partner, governments of both countries have expressed a desire to preserve the deal in the post-Brexit era. Therefore, it is not unlikely that the U.K. and Canada will use CETA as a basis for negotiations to sign another very similar deal to maintain the trading benefits once the U.K. exits from the EU.

CANADA'S IMPORTS FROM THE EU



10% Pharmaceutical Products
19% Machinery and Appliances
14% Motor Vehicles
7% Electrical Equipment
5% Minerals
45% Other

CANADA'S EXPORTS TO THE EU



4% Pharmaceutical Products
33% Precious Metals/Stones
9% Machinery and Appliances
8% Aircrafts & Spacecrafts
7% Ores
39% Other

Based on 2016 data from Government of Canada

YAZAN SALEH is an associate analyst on the Global Market Access (GMAS) Insights team at Decision Resources Group (DRG). He is responsible for monitoring the evolving healthcare and pharmaceutical landscapes with a focus on Canada, China, Japan, Saudi Arabia, and South Africa.

More Gender-Based Analysis Needed In Medical Device Studies

ANN NEUER Contributing Writer @anwriter

New research from Yale and the University of California San Francisco reveals that few medical devices are analyzed for the impact of gender on safety and effectiveness. It is widely known that women, as well as elderly and minority populations, have long been underrepresented in clinical trials for drugs and biologics, but as reported in *JAMA Internal Medicine*, a new study found a similar pattern when it comes to evaluating medical devices. The researchers reviewed 82 studies filed in 2015 with the FDA in support of premarket approval for original medical devices. Of the 77 studies that included both men and women, only 17 percent were analyzed by sex.

This finding is concerning given previous work that documents some stark differences between men and women in how medical devices perform. For example, women who received a particular left ventricular assist device for severe heart failure, known as the Thoratec HeartMate II, had a threefold higher rate of stroke as well as higher rates of infection and bleeding than men in the pre-approval studies. Similarly, women who undergo total hip replacement surgery have a 29 percent higher rate of hip implant failure as compared to men. This is the result of a study that analyzed 10 years of data from the largest total joint replacement registry cohort of elective primary total hip replacement in the United States.

> *"Devices sometimes work differently in men and women and have different safety and efficacy profiles."*
>
> **SANKET DHRUVA, M.D.**
> Cardiologist, Yale University School of Medicine

Sanket Dhruva, M.D., a cardiologist at Yale University School Of Medicine and a co-author on the new study, has extensively studied the lack of women-specific data in medical device clinical trials. He comments, "A key reason why we don't have more information about how medical devices perform in women is because these additional analyses are not always prioritized. Clinical trials are expensive to run and time-consuming, so the goal often becomes simply to see whether or not the device works. But we know that stratifying outcomes by sex can provide helpful insights."

Also, Dhruva points out that continual underrepresentation of women in clinical trials fuels situations whereby, even if gender-based analyses were to be performed, results would have little clinical significance as the studies are often underpowered. "This means that there are too few women in some studies to draw meaningful and reliable conclusions about a device's efficacy and safety," Dhruva explains.

Earlier research supports Dhruva's contention. One study of implantable cardioverter defibrillators (ICDs) in women highlighted how those randomized clinical trials were frequently underpowered. That article compared survival rates between women and men hospitalized for heart failure and implanted with a primary prevention ICD. These studies generally enrolled mostly men and were insufficiently powered to determine benefits in women, who represented just 10 percent to 30 percent of enrolled subjects.

Initiatives to bring more women, as well as minorities and the elderly, into clinical trials have been a major focus of the FDA, as evidenced by legislation and guidance. One of the efforts is the Medical Device User Fee Amendments, which Congress reauthorizes every five years, and which had a Sept. 30, 2017 deadline. The Amendments are part of the 2012 Safety and Innovation Act, which contains Section 907, a discussion on better inclusion of demographic subgroups in medical product applications submitted for marketing approval.

On August 3, the Senate passed a bi-partisan bill for the reauthorization, following the House's lead, where the bill passed in July. This action coincides closely with the release of Dhruva's study. "There is some momentum from the FDA's recommendations to improve the completeness and quality of analyses of data on demographic subgroups in summaries of product safety and effectiveness data and in labeling, but we need to do a lot more," he remarks.

Information Management Strategies To **Improve Data Integrity During M&As**

KIP WOLF

Merger and acquisition integration presents great challenges to maintaining business continuity, transferring appropriate knowledge, and transferring information assets in a timely and effective manner. By starting with the end in mind and engaging the entire integration team early (i.e., before the contract closure), the change-management activities and education/maturation of information management practices will greatly reduce these risks and challenges, and will significantly increase the probability of successful business continuity during and after M&A.

The FDA has long been concerned about data integrity. From the advent of 21 CFR Part 11 in 1996 to the most recent FDA Draft Guidance on Data Integrity, the accuracy and consistency of data used in life sciences has been a focus of regulation and related inspection both in the U.S. and most other major biopharmaceutical markets.

As business strategies are defined and implemented with the inclusion of M&As, which seem to be only increasing in recent years, data integrity represents a critical risk to the probability of successful M&A. Due diligence for M&A is rarely sufficient to uncover operational-level risks that present real threats to (for example) integration of manufacturing operations, business continuity, and continuous supply of life-saving therapies.

In one recent M&A-related project, manufacturing operations of a top-10 biopharmaceutical company were potentially threatened by complications in identifying all regions where recently acquired assets were registered for commercial market. While both the acquiring and the acquired companies managed their regulatory data effectively, the disparity in information technology systems, roles and responsibilities for information, and data definitions presented sufficient differences that caused confusion and (at a minimum) minor delays in product release while details were sorted out. While this is not unusual during the initial months (and in some cases, years) after "Day 1" of a merger, the challenges can be reduced and the risks mitigated with increased effort on data integrity in the early days of M&A discussion, strategy, planning, and integration.

Too often we see IT systems and related data discounted to a few line items on a due diligence report or integration plan. It is very common to behave in a reactive mode during M&A, where the deal is done and the attention to data integrity applied too little and too late to make an effective and efficient difference to the final company integration. Underestimating the resources required inevitably compounds the resources assigned to perform data verification and cleanup activities after "Day 1," but it doesn't have to be this way.

AN OUNCE OF PREVENTION

Data integrity involves much more than information technology systems and data definitions. Data integrity starts with a culture of understanding information as a vital company asset. Only by truly understanding the quality culture of an organization can we plan appropriately for the integration of cultures and information during M&A.

By making a disciplined and intentional assessment of how a culture manages its data early in the M&A life cycle, much confusion and risk can be avoided. Leaders in business development should take a look at information priorities between the acquiring and the target companies as early as possible and engage functional areas like regulatory, QA, and legal during the early due diligence stage. It is far less disruptive to make adjustments in perspective, priority, and management of information before IT system integration begins, than to wait until integration starts and pass that responsibility on to the resources who are tasked with merging great amounts of disparate data.

By engaging the entire M&A integration team early to align expectations for knowledge transfer and data/document transfer, the probability of successful business continuity is significantly increased. Use tools like process mapping, data diagrams, and information models early to help key employees understand how and when data is created and managed. In doing so, disparities may be identified and resolved long before the IT systems begin to merge. In some cases, cultural change is necessary to (for example) shift responsibilities for data management from one level or one department to another. Modifying the operations even before the IT systems are merged can ensure better understanding, integration and adoption, and uninterrupted business operations.

> *"Too often we see IT systems and related data discounted to a few line items on a due diligence report or integration plan."*

DATA INTEGRITY IS ABOUT CULTURE

Strong data integrity is the result of a cultural norm that identifies information as a vital company asset — and permeates every operation in the organization. From document control, to management of raw analytical data, to the execution of batch records on the manufacturing floor, data integrity is elevated through a strong quality culture. Assessing this early in M&A activities ensures better preparation for mitigating risks when (not if) issues arise.

The biopharma companies that exhibit the strongest data integrity have taken the culture seriously enough to implement offices of Information Governance under IT. These groups are sometimes organizationally aligned with IT departments and other times integrated in business functions. Regardless of the organizational location, they are always most successful when the members of these groups represent cross-functional, cross-divisional interests. As members of these groups learn the operations of the functional areas that they represent and become trusted advisers of, and advocates for, these areas, value is realized in reduced confusion, less information conflict, and improved operational efficiencies (e.g., by reducing defects in data transactions from function to function).

Personnel management and personal development also involve critical success factors for strong data integrity during M&A. Very understandably, the personnel of an acquired company may feel anxious about their future and very insecure in their roles and responsibilities. For this reason, a proactive effort is needed to identify early on the information owners and critical stakeholders in the acquired company and to engage them in the planning of, and activities for, integration. This early effort results in a much more successful transfer of information assets and alignment of operations. Likewise, adding data integrity-related topics and continued education to the job descriptions, role curriculum, and personal development plans of information owners and critical stakeholders has resulted in great improvements in data integrity. Results have included reduction in the number and severity of deviations, improved clarity and efficiency in processes, and increased adherence to supply chain plans (to name a few).

When data integrity concepts are successfully embedded at every level of an organization, the business matures to a level of strategic alignment that produces self-correcting results and ensures a greater avoidance of risk. While these results may improve integration of the acquiring and acquired company operations and ensure business continuity during M&A, they also ensure the highest probability of meeting demands for patient therapies and increasing shareholder value. L

KIP WOLF is a senior managing consultant at Tunnell Consulting where he leads the data integrity practice. He has more than 25 years of experience in the fields of quality assurance and regulatory affairs, GMP and IT compliance, technical operations, and product supply.

Competitive Advantage Is Not What It Used To Be

RITA GUNTHER MCGRATH

RITA GUNTHER MCGRATH is a globally recognized thought leader who focuses on leading innovation and growth, working with senior executives to think strategically, even in today's rapidly changing and volatile environments.

The pharmaceutical and healthcare industries are at a crossroads, with the traditional business models experiencing what some have described as "fatigue." Like many other industries facing profound shifts, this creates the imperative to bring together the disparate fields of competitive strategy, innovation, and organizational change.

We need to add new frameworks and tools for practicing strategy to the well-entrenched ones many of us are still using, because the boundary conditions have utterly changed. What use is a five-forces analysis, for instance, when firms can be both buyers and suppliers simultaneously? How valuable is industry analysis when the most significant competition crosses industry lines?

THE NEW STRATEGY PLAYBOOK

The implications of all these ideas come together in what I refer to as a new playbook for strategy. Strategy today needs to be based on the idea of transient competitive advantage — that is, where you compete, how you compete, and how you win is very different when competitive advantage is no longer sustainable for a long period of time. The new playbook encompasses:

1. Continuous organizational reconfiguration so the organization doesn't get stuck in bureaucracy
2. Healthy disengagement when the time comes
3. Deft resource allocation so people and funds go to their best opportunities rather than being held hostage in often-competing organizational silos
4. Innovation as a genuine proficiency, throughout the organization
5. Courageous leaders who realize you can't manage a secret
6. Talent strategies that fit a "tour-of-duty" world

The good news is that we have developed a number of new tools and frameworks that are suitable for this higher-velocity, uncertain environment.

NEW TOOLS FOR INNOVATION

For instance, when it comes to assessing and selecting projects, we know that including option value (the value of a right to make a future choice) can counter the pervasive anti-innovation bias of innovation killing tools such as net present value. It also allows you to invest in the future without risking massive losses.

We also understand much better how to use intelligent failure to facilitate learning. In fact, rather than calling them failures, I'd encourage you to think of them as investments in learning, much in the same way we invest in experiments in science. Even when a hypothesis is not borne out, it teaches us what avenues are likely not to be fruitful, which has value.

Opportunity recognition is a skill that can be enhanced and developed in a systematic way, as can the other elements of innovation proficiency, such as incubating new projects and accelerating their growth.

Although the old competitive rules in the life sciences and healthcare spaces are changing, with those changes also comes tremendous opportunities — if leaders learn to capitalize on them.

Be sure to check out the archive of Leadership Lessons on our website at lifescienceleader.com/resource/leadership-lessons. There you will find five years' worth of columns by some of the top leadership gurus.

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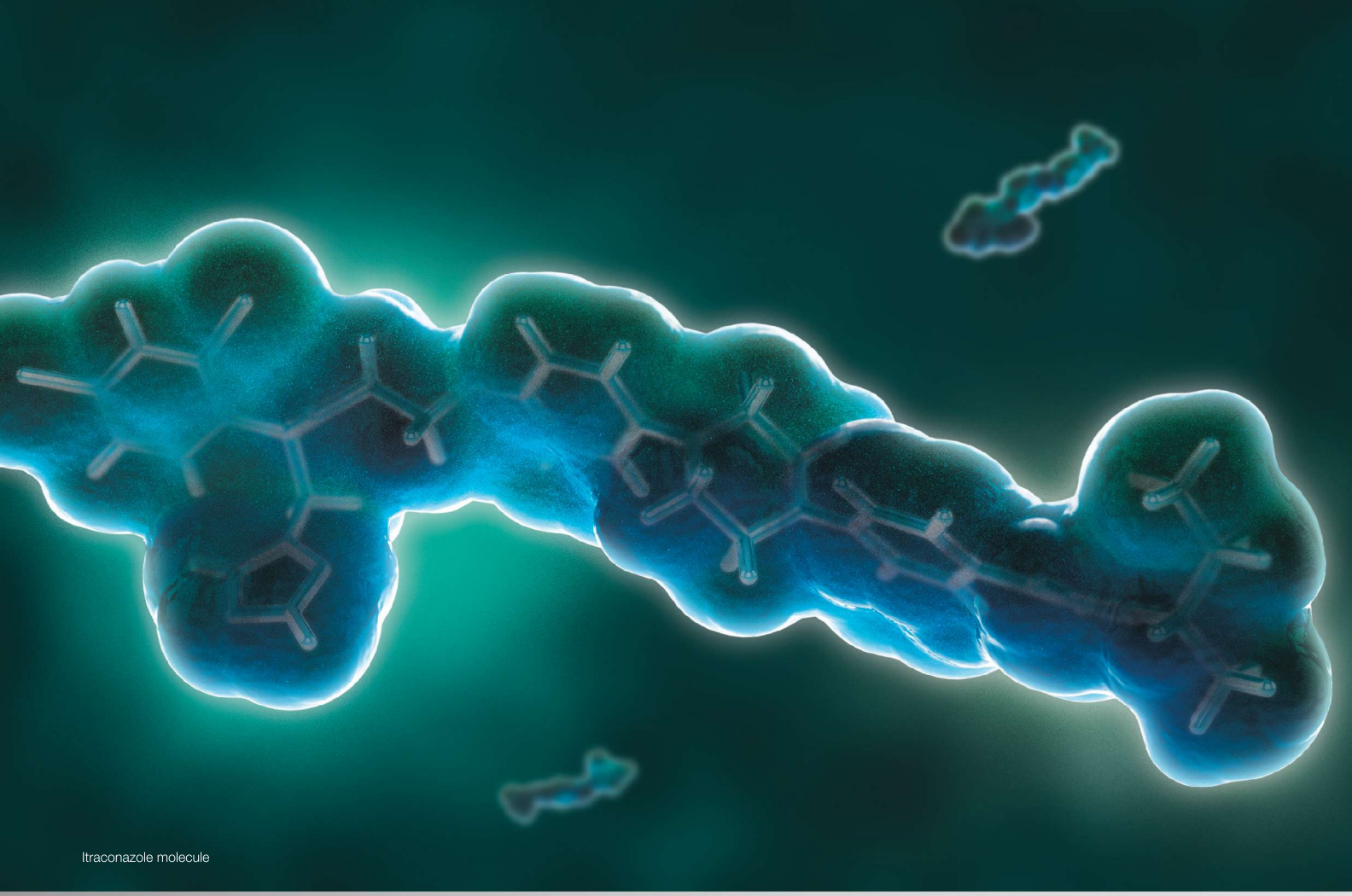

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